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PREFACE

The authors in this third *Review* have continued to support the principal design set by their predecessors. This design has been that each section shall be written by an authority in the field concerned, and that it shall be a discussion of the subject in the light of contemporary literature and the author's special knowledge, rather than a cataloguing of references or stringing together of abstracts. Once again, we thank these authors for their thoughtful rendering of a task that is never easy.

Due to space limitations imposed shortly after the authors for this volume were selected, it was necessary to delete two reviews originally planned for this year. Doctor Ferrebee kindly put his paper on allergy over for Volume 4, and the Editor withdrew his section on therapeutics Unfortunately, at the last minute, the manuscripts of Doctors J. S. L. Browne on endocrinology, E. C. Reifenstein, Jr. and R. P. Howard on diseases of bones and joints, and G. W. H. Schepers on diseases due to physical agents and trauma could not be completed, and we must look to future volumes for consideration of these subjects.

The Editors are most indebted to the Annual Reviews office staff, particularly Carol F. Kupke, Robbie Bass, Phyllis F. Dexter, Gwen Eagle, and Liselotte B. Hofmann, for their close surveillance of what goes on the printed page.

J.S.L.B E M.MacK.
A.M.B. S.C.M.
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W.C.C.

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INFECTIOUS DISEASES[1]

THE EFFECTS OF CORTISONE AND ADRENOCORTICOTROPIC HORMONE ON INFECTION

By LEWIS THOMAS[2]

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The most notable advance in the field of infectious disease during the period covered by this review has been the discovery, in many quarters, of the remarkable effects of cortisone and adrenocorticotropic hormone (ACTH) on the process of infection. Indeed, although it is highly improbable that the therapeutic properties of these substances in infectious disease will be in any sense comparable to those of antibiotic and chemotherapeutic drugs, they provide investigative tools which will perhaps contribute much more to our understanding of basic problems in infection. Such difficult matters as the role of the host reaction, the meaning of natural resistance and susceptibility, mechanisms involved in tissue damage and infection, and the relationship between the tissue responses to bacteria, viruses, and bacterial toxins now seem to be experimentally approachable. This is one reason for the selection of this subject for the present review Another is that the use of these materials in medicine has now moved well beyond the stage of experimental study in special clinics, they are now in daily use as remedies in hospital and home practice throughout the country. Their general acceptance as therapeutic agents preceded the prolonged period of animal experimentation which, in the past, has usually occurred before application of new drugs in human disease. Information which is beginning to come from work with animals has important and disturbing implications, and although much of it is available only in the form of preliminary reports, the critical attention of clinicians is warranted at the present time (1, 2, 3).

Following the successful introduction by Hench and his co-workers (4) of the use of cortisone and ACTH in rheumatoid arthritis, and the subsequent application by others to numerous, wholly unrelated disease states ranging from severe burns to gout, clinical trials of the materials in infectious diseases were inevitable The first reports of their use in pneumonia, by Finland and his collaborators (5), aroused widespread interest. These workers described the effects of ACTH on the course of acute pneumococcal pneumonia and primary atypical pneumonia, in each case there occurred a rapid and apparently beneficial response, with defervescence of fever and clear cut improvement in the symptoms and signs of the disease. In each instance,

[1] The survey of the literature pertaining to this review was concluded in September, 1951

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however, there was a conspicuous discrepancy; the patient with pneumococcal pneumonia was found to have bacteremia during a two day period after ACTH had apparently improved his state, and the patient with primary atypical pneumonia resumed the typical course of her disease as soon as ACTH was stopped. The therapeutic effect of cortisone in typhoid fever was studied by Smadel (6), Woodward (7), and their co-workers. Here, as in pneumonia, there was a rapid and dramatic improvement in the subjective symptoms of the disease, as well as a prompt fall in temperature; however, typhoid bacilli were cultured after the apparent clinical improvement, and relapse and complications were not prevented.

As other reports on the use of ACTH and cortisone in human infectious disease entered the literature, and as supplies became more easily available for animal experimentation, evidence began to accumulate which indicated that these materials might cause adverse effects in some types of infection. At the present time the most substantial portion of the evidence is derived from animal studies, and it will be reviewed in the section which follows. The available information concerning the effects on human infection will then be discussed.

The Effects of Cortisone and Adrenocorticotropic Hormone on Infection and Immune Reactions in Animals

Tuberculosis.—In 1949, Lurie and his associates (8) suggested that adrenal cortical hormones were in some way responsible for resistance to infection by tubercle bacilli, on the basis of the observation that genetically resistant strains of rabbits consistently developed hypertrophy of the adrenal cortex in response to infection while susceptible strains did not. In order to test this concept, groups of rabbits were treated with cortisone and infected with virulent human-type tubercle bacilli by the inhalation method of Lurie (9). Cortisone was injected on alternate days in a dosage of 2 mg. per kg., and infection was induced three days after the beginning of cortisone treatment. The animals were sacrificed after approximately seven weeks, and the number and size of pulmonary tubercles determined. The lungs of the cortisone treated animals were found to contain four times as many tubercles as in the controls, and microscopic study revealed "a far greater number of living tubercle bacilli in the lungs of the cortisone rabbits" than in the lungs of the controls On the other hand, the dissemination of bacilli to the tracheobronchial lymph nodes appeared to be less extensive than in the control animals The authors expressed the opinion that the effect of cortisone might be due to an increase in the degree of phagocytosis and consequent limitation of the infection within the lungs, and they postulated a relationship between the effect of cortisone and the mechanism of genetic resistance in rabbits (10).

More definite evidence of an adverse effect was obtained by Spain & Molomut (11), who tested the effect of cortisone on the development of tuberculous lesions in guinea pigs. They employed a d

sone daily, beginning 16 days after infection and continuing for a total of 28 days. In the treated guinea pigs, the tuberculous lesions were more extensive, less well organized, and more widely distributed through the body than in untreated controls. Streptomycin was partially effective in controlling the infection, but nodular tuberculous lesions appeared despite streptomycin therapy when cortisone was discontinued. They concluded that resistance to tuberculous infection is markedly decreased by cortisone.

Michael, Cummings & Bloom (12) demonstrated that the rat, a species which is naturally resistant to tuberculosis, becomes highly susceptible to this infection following treatment with cortisone. These workers treated albino male Sprague-Dawley rats with 5 mg. of cortisone daily and infected the animals by an intraperitoneal injection of tubercle bacilli. Control groups of animals were included in which cortisone was given without infection and infection was produced without cortisone The experiments were terminated after 42 days or longer. The results were clear-cut. None of the infected animals died in the control group which did not receive cortisone. In the group which was given cortisone without infection, three rats out of 15 died In contrast, of 20 rats treated with cortisone and infected with tubercle bacilli, 16 died.

The pathological findings in these animals were of considerable interest. The untreated infected rats showed enlargement of the spleen and many well-organized tubercles containing a few acid-fast microorganisms in the lungs. The cortisone-treated infected animals showed extensive areas of pneumonitis and caseation; in one instance the caseous mass involved not only the entire lung but also invaded the chest wall. There was no apparent attempt at tubercle formation and numerous bacilli were observed throughout the lungs, in the alveolar exudate and in the interstitial tissue. The spleens of the treated animals were not enlarged, but showed depletion of the lymphoid elements and numerous free acid-fast bacilli The authors suggested that the depression of resistance to infection might be explained on the basis of the suppressive effect of cortisone on lymphocytes

D'Arcy Hart & Rees (13) reported comparable results with experimental tuberculosis in mice. Under the influence of cortisone treatment, in a dosage of 0.25 to 0.5 mg daily, the mortality of infected mice was markedly increased, and the lesions were larger, more necrotic, and showed many more bacilli than in untreated controls

Pneumococcal infection—Kass and his co-workers (14) investigated the effects of ACTH and cortisone on pneumococcal infection in the mouse. These workers employed ACTH in a daily dose of 5 mg divided into two injections at 12-hr. intervals; cortisone was administered in an initial dose of 10 mg followed by single daily doses of 5 mg. A virulent Type 2 *Pneumococcus* was used for infection by the intraperitoneal route. ACTH was found to have no effect on the mortality, although the treated animals tended to survive for slightly longer periods of time. In the cortisone-treated group, however, the mice died more rapidly than controls In another communica-

tion (15), these authors present evidence for the extremely high resistance to the hormonal effect of ACTH in mice; it is possible that the differences observed between ACTH and cortisone may have been due to this resistance.

Robinson (16) obtained more definite evidence for the enhancement of pneumococcal infection by cortisone in rabbits. In his experiments, cortisone was administered daily for seven days prior to infection, in a dose of 1 to 3 mg. per kg. body weight, and continued in similar doses until the end of the experiment. In control animals without cortisone, the strain of Type 1 *Pneumococcus* employed was relatively avirulent, with transient low grade bacteremia and survival in most animals. In the cortisone-treated rabbits extensive pneumococcal bacteremia occurred in the majority of instances and was followed by death within 4 to 10 days. The skin lesions produced by intradermally injected pneumococci were markedly altered by cortisone treatment In control animals sharply localized skin lesions were produced, measuring approximately 3 to 4 sq. in. after 48 hr. In the cortisone-treated rabbits the dermal lesion measured approximately 28 sq. in. Penicillin was found capable of controlling the infection in cortisone-treated rabbits, but much larger doses were required than for the control of pneumococcal infection in untreated rabbits.

Glaser and his associates (17) performed similar experiments in rats, employing the intrabronchial route for the infection with pneumococci. The animals were treated with cortisone for five days prior to infection and for varying periods thereafter. Survival rates were less favorable in the treated group than in control rats, and a striking difference in the histological appearance of infected lung tissue was observed. In the cortisone-treated animals, the lungs contained a considerable amount of acellular edema fluid in which there were many more bacteria than were ever seen in analogous lesions from control animals The authors attributed the extraordinarily large bacterial population and the sparsity of inflammatory cells in the lung tissue to a delay in the diapedesis of leukocytes The phagocytic activity of the few leukocytes which were present in the lesion did not appear to differ in the cortisone-treated animals from that observed in the lungs of untreated rats.

White & Marshall (18) obtained comparable results in pneumococcal infections of rabbits These workers gave cortisone in a daily dose of 15 to 20 mg for two days before and after the intravenous injection of suspensions of pneumococci and compared the extent of bacteremia with that in an untreated control group. A striking difference was evident within a few hours after infection, in the control series the number of organisms fell rapidly and the animals recovered, while the cortisone-treated rabbits showed a steady increase in septicemia which resulted in death within 24 to 48 hr

Treponema infection.—Cortisone was shown by Turner & Hollander (19) to cause a marked alteration in the appearance of the lesions of experimental syphilis in rabbits. During treatment with cortisone, excessive amounts of mucoid material appeared in the lesions and unusually large numbers of treponemes were demonstrable. When treatment with cortisone

was stopped the lesions rapidly increased in size, attaining dimensions never encountered in untreated rabbits.

Brucella infection.—Abernathy (20) has reported that the clinical course and tissue reactions of experimental brucellosis in mice, guinea pigs, and rabbits were changed under the influence of cortisone treatment. Groups of animals undergoing acute and chronic infection with various strains of *Brucella* were treated with cortisone for periods of five to fourteen days. The death rate was higher than in untreated controls, and the tissue lesions were more widely distributed throughout the body. The characteristic hepatic granulomata of brucellosis were converted into ill-defined areas of extensive necrosis; this was most marked in infections caused by *Brucella suis*

Streptococcal infection.—The effects of cortisone on infection with Group A hemolytic streptococci in rabbits were studied by Mogabgab & Thomas (21). Rabbits weighing approximately 2 kg were treated with cortisone in a daily dosage of 12 mg. for three days prior to infection and for variable periods thereafter. Infection was induced by an intradermal injection of varying numbers of Group A streptococci suspended in broth. A control series of rabbits which did not receive cortisone were similarly infected Streptococcal bacteremia and death occurred in 71 of 76 rabbits which were treated with cortisone In contrast, of 86 infected control rabbits which did not receive cortisone, only six developed bacteremia and three died In most of the cortisone-treated group, blood cultures became positive 24 hr. after the intradermal infection, and colony counts of the blood revealed a steady increase in the extent of bacteremia until the day of death The majority of animals died between 4 and 12 days after infection, and at the time of death some of these animals had colony counts as high as 100,000 microorganisms per cubic centimeter of blood The existence of severe bacteremia did not appear to effect the general appearance, activity, or appetite in many of the cortisone-treated rabbits until shortly before death Hematological studies showed a fall in the lymphocyte count during treatment wth cortisone After bacteremia became demonstrable, there was also a fall in the polymorphonuclear leukocyte count, elevation of the sedimentation rate, and marked lowering of the hematocrit No difference in the phagocytic activity of leukocytes from cortisone-treated and normal rabbits was demonstrable The effect of cortisone on streptococcal infection was not modified by the administration of desoxycorticosterone and salt, nor by nitrogen mustard Penicillin in very large doses (400,000 I.U. per day per rabbit) caused recovery of the majority of cortisone-treated rabbits when given within three days after infection.

ACTH, in a dose of 5 mg per kg. every 6 hr., produced streptococcal bacteremia which was in every way comparable to that observed with cortisone When rabbits were immunized with streptococci prior to the institution of cortisone-treatment and infection, bacteremia was observed for only brief periods, or not at all, and the majority of the animals survived, indicating that enhancement of infection by cortisone did not involve inter-

ference with the protective function of antibody (22). It was also found that the protection provided by immunization was apparently not dependent upon the M-substance of the *Streptococcus*, since immunization with one Lancefield type of *Streptococcus* provided protection against infection by unrelated types in cortisone-treated rabbits.

In the cortisone-treated rabbits which died within four days after infection with streptococci, very dense accumulations of cocci were visible in histological preparations of heart tissue. In animals which died seven days or longer after infection, such deposits of cocci were not seen, but occasional foci of myocardial necrosis and inflammation were present in the heart.

When cortisone was discontinued on the day following streptococcal infection, the majority of rabbits survived, although all exhibited positive blood cultures for four or five days Scattered, small inflammatory lesions were encountered in the hearts of some rabbits when sacrificed a week after infection, suggesting that cardiac involvement by streptococci may have occurred during cortisone-induced infection. This was further supported by the finding that an intravenous injection of gram negative bacterial toxin, capable of provoking the Shwartzman reaction (see below) resulted in acute hemorrhagic necrosis in the hearts of these animals when given four days after infection (23). At the same time, typical Shwartzman reactions occurred in the skin at the site of the original intradermal injection.

Typhoid bacillus infection—Normal rabbits possess a high degree of natural resistance to infection by typhoid bacilli, regardless of the route of infection Watson & Cromartie (24) have recently demonstrated that this resistance is lost during treatment with cortisone. These authors administered cortisone in a daily dose of 15 mg. per rabbit and injected suspensions of typhoid bacilli intradermally on the third day of treatment Cortisone was continued in the same dosage until death of the animals. All of the treated rabbits developed positive blood cultures and died within eight to ten days after infection Control animals infected in the same fashion survived without demonstrable bacteremia.

Spontaneous bacterial infections—Several authors have commented on the occurrence of multiple abscess formation and septicemia in animals during the course of prolonged treatment with ACTH or cortisone. Antopol (25), in a study of the anatomic changes produced in mice by large doses of cortisone, described the occurrence of granulomatous nodules in the liver, kidney, and spleen from which *Corynebacterium pseudotuberculosis murium* was cultured in 8 of 19 mice following six days of treatment with cortisone. Selye (26) reported the frequent occurrence of pulmonary abscess formation and generalized septicemia in animals treated with either cortisone or ACTH in large dosage, attributed to varieties of microorganisms ordinarily considered to be nonpathogenic. The latter worker stated that this effect of cortisone and ACTH was completely prevented by the administration of pituitary somatotropic hormone The reviewer has encountered four instances of fatal septicemia in rabbits within three days after beginning cortisone

treatment; the responsible microorganism, *Salmonella typhimurium*, was also cultured from the feces of these animals (22). Cavallero (27) treated 51 rats with varying doses of cortisone for periods of two to eight weeks and encountered spontaneous infections in 27 animals of the group; the infections were caused in most instances by *Pasteurella muricida* and were characterized by disseminated areas of necrosis in the spleen, liver, and lungs.

Wolf and his co-workers (28) reported the activation of trypanosomiasis in 12 of 39 *Macacus rhesus* monkeys during tests of the effect of cortisone on experimental allergic encephalomyelitis. Nine additional animals exhibited lesions compatible with trypanosomiasis but without demonstrable parasites. Encephalomyelitis and myocarditis were present in the monkeys with proven trypanosomiasis. These animals had received cortisone in daily doses ranging from 5 to 40 mg. Untreated control monkeys in the same colony showed no trypanosomal lesions, although parasites were demonstrated in the blood of two

Fungus infection.—The effect of cortisone on the course of infection with experimental ringworm in guinea pigs was studied by Kligman and co-workers (29). Twelve animals were given a subcutaneous injection of 5 mg. of cortisone for 10 days prior to infection, six received a similar daily dose beginning on the day after infection, and six were treated with cortisone when the skin lesions became prominent. In all of the cortisone-treated animals there was a somewhat delayed incubation period before the appearance of visible lesions, but the lesions were similar in their general appearance to those in control untreated guinea pigs. However, the fungi were detectable in skin scrapings for a significantly longer period in the treated animals, and healing of the lesions was delayed for as long as three weeks as compared with the controls.

Sutliff & Norman (30) described an apparent aggravation of the local inflammatory lesions of cutaneous blastomycosis in human beings Their observations will be discussed in the section dealing with human infection. Jadassohn *et al* (31) studied the infection of guinea pigs by *Achorion Quinckeanum.* Cortisone in a daily dose of 15 mg. had no demonstrable effect upon the time of incubation or the appearance of the lesions in the skin caused by this agent.

The experimental infection of rats with C[illegible]

by [illegible]

firm [illegible]

infection In five cortisone-treated rats, a diffuse systemic infection involving large areas in the lungs and spleen occurred. The authors commented on the apparent inhibition of connective tissue proliferation in the infected tissues of the treated rats.

Virus infections—The earliest indication that cortisone might have an enhancing effect on virus infections was reported by Shwartzman (32), employing poliomyelitis virus (strain MEFI). The incubation period produced by this agent in untreated mice was between eight and twelve days.

In mice which were treated with a combination of ACTH and cortisone, the incubation period was shortened to two to four days, and death occurred at a correspondingly earlier time after infection. More remarkable results were obtained with Syrian hamsters. This species is ordinarily quite resistant to infection by poliomyelitis virus, with a low incidence of established virus infection and a very low mortality rate. When hamsters were treated with cortisone or with a combination of cortisone and ACTH prior to the intracerebral injection of virus suspensions, a severe and uniformly fatal paralytic disease developed within two days after inoculation. Poliomyelitis virus was identified in the brains of these animals by passage to susceptible mice and by appropriate neutralization tests The administration of ACTH alone failed to produce any enhancement of poliomyelitis infection in either mice or hamsters, and the author suggested that this failure might be due to the stimulation by ACTH of an adrenal cortical factor "capable of reversing the enhancing effect of cortisone " However, the data presented did not support this concept, since the simultaneous administration of ACTH and cortisone was quite as effective as the administration of cortisone alone.

Karnofsky and co-workers (33) have demonstrated that cortisone produces profound effects on the growth and development of the chick embryo The possibility that such changes might be associated with an alteration in resistance to virus infection was investigated by Kilbourne & Horsfall (34), employing two strains of influenza virus and one of mumps virus. These workers injected varying amounts of cortisone into the yolk sac of 10-day old embryonated eggs, followed by the intra-allantoic inoculation of virus. After incubation the concentration of virus in allantoic fluid and embryonic tissues was estimated by infectivity titrations as well as by determinations of hemagglutination titer A consistently increased amount of virus was demonstrated in the eggs which had been injected with cortisone, indicating a marked enhancing effect of this material on the proliferation of mumps and influenza viruses. It is of incidental interest that these authors also noted the embryo-stunting effect previously described by Karnofsky (33) following the injection of cortisone

The Coxsackie group of viruses possess in common the unique property of being virulent for newborn or suckling mice and hamsters but avirulent for adults of the same species (35). Indeed, this characteristic is the only biological point of similarity between the agents in the group. Kilbourne & Horsfall (36) have recently demonstrated that treatment of adult mice with cortisone renders them quite as susceptible as immature animals to Coxsackie virus infection. These authors administered a single subcutaneous injection of cortisone in a dosage of 2.5 to 5.0 mg. in 16-gm. adult white mice and, within 1 or 2 hr thereafter, injected a suspension of Coxsackie virus by the intracerebral route. Three days after infection all of the animals were dead, and large concentrations of Coxsackie virus were demonstrated in their brains by subsequent passage to suckling mice. Control adult mice given the same inoculations of virus remained well and uninfected. By

increasing the dose of cortisone to 7.5 mg., lethal infection was established in older mice weighing 35 gm. each. The use of cortisone enabled the authors to isolate and identify Coxsackie virus from human feces in fully developed mice, an accomplishment which had never previously been possible except in newborn or suckling animals. It was also observed that the incubation period in the cortisone-treated animals was much shorter than that usually observed in untreated suckling mice. Moreover, it was possible to establish lethal infections with virus injected by the intraperitoneal route in adult mice when cortisone was administered. Serial passage of two strains of Coxsackie virus through cortisone-treated adult mice was carried out, and it was shown that the viruses passed in this fashion did not become adapted to untreated adult mice. These results, like those described above with bacterial infections, indicate that the effect of cortisone is exerted upon the host and not upon the infecting agent itself.

Bacterial and viral toxins—It has long been recognized that adrenalectomized animals are more susceptible to the lethal effects of a variety of bacterial toxins than are normal animals Lewis & Page (37) reported that this increased susceptibility could be prevented by the administration of adrenal cortical hormone, and they utilized this as a method for the assay of substances with hormone activity. Kass and his co-workers (38) were unable to demonstrate any protective effect by ACTH against the toxic properties of suspensions of rickettsiae or influenza viruses in mice or rats. It should be noted that these experiments were carried out with intact animals with normal adrenal function and are therefore not comparable to the experiments of Lewis & Page. Kass & Finland (39) showed that the febrile reactions of rabbits to injections of typhoid vaccine were reduced by treatment with ACTH; it is doubtful that this antipyretic effect of ACTH can be regarded as protection against bacterial toxin.

The Shwartzman phenomenon (40) is an experimental model which serves, in a sense, as a prototype for the mechanism of necrotizing tissue damage by many infectious agents If cortisone and ACTH possess general protective properties against bacterial endotoxins, it might be expected that they would prevent this reaction. The available reports dealing with the subject are contradictory The phenomenon is produced in rabbits by an intradermal injection of gram negative culture filtrate, followed 24 hr later by the intravenous injection of similar material. The reaction consists of extensive hemorrhagic necrosis at the "prepared" skin site, which develops within 1 to 2 hr after the intravenous injection of toxin The mechanism of the phenomenon is not understood although numerous hypothesis have been proposed There is evidence that a cardinal feature of the prepared skin tissue is the accumulation and production of abnormal amounts of lactic acid (41), participation of polymorphonuclear leukocytes and platelets in the reaction has been suggested because of its inhibition by nitrogen mustard and the failure of such inhibition when bone marrow is protected against the action of mustard (42); Stetson (43) has recently presented evi-

dence which indicates that thrombosis by agglutinated leukocytes and platelets within the small blood vessels of the prepared area may be an initiating factor in the phenomenon.

Soffer, Shwartzman, and their co-workers (44, 45) have reported that the Shwartzman phenomenon is inhibited by the administration of ACTH or cortisone. The minimum effective dose of ACTH was 12.5 mg. per rabbit, and it was necessary to inject the material 2 hr. prior to the intravenous or "provocative" injection in order to bring about inhibition; when the same amount of ACTH was given 2 hr. prior to the preparative intradermal injection, no inhibition of the phenomenon occurred. The results with cortisone indicated that relatively enormous amounts of this substance were necessary in order to bring about inhibition, and in no instance was inhibition produced in all animals tested. In fact the authors have stated that no significant inhibition was observed when 40 mg. of cortisone were injected intramuscularly 2 hr. before the intravenous injection of toxin, only partial inhibition resulted from the injection of 75 mg. at this time, and 60 mg. injected 4 hr. before the intravenous injection failed to inhibit. With material as insoluble and slowly absorbed as cortisone, one would expect a greater biological effect after 4 hr than at 2 hr , yet the contrary was observed. The possibility that some of the effects attributed to cortisone may have been due to the suspending agents employed in commercial cortisone preparations was not excluded in the data presented.

Results which were not in agreement with the foregoing were obtained in experiments utilizing saline suspensions of crystalline cortisone by Thomas & Mogabgab (46) and Thomas & Good (47, 53). Rabbits were treated with 12 mg. of cortisone per kg. for four days, with preparation of the skin by bacterial toxin on the third day and intravenous injection of toxin on the fourth. An untreated group of rabbits was prepared and challenged with the same doses of bacterial toxin. In nine of the 10 animals in each group, typical Shwartzman reactions were elicited, indicating that under conditions of prolonged and excessive dosage with cortisone the Shwartzman phenomenon was not inhibited. During the course of these experiments it was noted that many of the prepared skin areas were markedly different in appearance from those in control untreated rabbits. During the first 12 hr after the intradermal injection of toxin no local reactions were visible, while in the controls erythema and edema appeared at the site of injection within 4 hr. After 18 to 20 hr. there was still no edema in the treated rabbits, but many small petechiae were noted within an area of skin equivalent in size to the inflamed area in the controls. When the intravenous injection of toxin was [illegible]

vessels in the subcutaneous tissue, a moderate degree of inflammatory reaction with an exudate chiefly composed of polymorphonuclear leukocytes,

and hemorrhage. At this stage of the development of the lesion, it was still possible to provoke a complete Shwartzman reaction by an intravenous injection of toxin, indicating that the "primary" response to intradermal toxin in cortisone-treated rabbits did not interfere with the Shwartzman phenomenon itself. Because of the general resemblance of this hemorrhagic skin lesion to the Shwartzman reaction, experiments were undertaken to investigate the effect of intravenously injected toxin in cortisone-treated rabbits (47). Cortisone was administered for a total of four days in a dose of 25 mg. per day, and on the third day a single intravenous injection of toxin derived from meningococcus cultures or *Serratia marcescens* extract was given in the ear vein. In approximately 70 per cent of the rabbits treated in this fashion, bilateral cortical necrosis of the kidneys developed within 24 to 36 hr. Hemorrhage and necrosis were also noted in the lungs, liver, spleen, and to a less extent in the gastrointestinal tract. Such lesions, particularly cortical necrosis of the kidneys, are characteristic of the so-called generalized Shwartzman reaction (48), which is produced by two successive intravenous injections of toxin spaced 24 hr. apart. Evidence was obtained which indicated that the mechanism of production of the lesions in the cortisone-treated rabbits was similar to that of the generalized Shwartzman reaction. Histologically, the lesions in the kidneys were indistinguishable. Nitrogen mustard, in a dose of 1.5 mg per kg., completely inhibited the generalized Shwartzman reaction and also prevented the development of renal necrosis in cortisone-treated rabbits (49). The protective effect of mustard was nullified in both groups when the femoral artery was clamped during the administration of this substance, a procedure which results in sparing a sufficient area of bone marrow so that polymorphonuclear leukopenia does not occur (50).

Although no explanation is available for these lesions, the results suggest that cortisone, in the dosage employed, has an effect which resembles one phase of the Shwartzman reaction. Hemorrhagic reactions in the skin or kidneys were never observed to occur in normal rabbits following single intradermal or intravenous injections of toxin; in effect, cortisone treatment accomplished the same end result as the second or "provocative" injection of toxin. In an animal heavily treated with cortisone, it has been observed repeatedly that much of the available lymphoid tissue undergoes dissolution (51, 52). In this circumstance it is conceivable that a mechanism which may be responsible for the removal of [illegible]

bearing directly on this point was obtained, but an observation which may be relevant to the problem was the following: a single intradermal injection of toxin in cortisone-treated rabbits consistently resulted in bilateral cortical necrosis of the kidneys (53). There is substantial evidence in the work of others (40) that toxins of this class are absorbed from the skin only to a very

dence which indicates that thrombosis by agglutinated leukocytes and platelets within the small blood vessels of the prepared area may be an initiating factor in the phenomenon.

Soffer, Shwartzman, and their co-workers (44, 45) have reported that the Shwartzman phenomenon is inhibited by the administration of ACTH or cortisone. The minimum effective dose of ACTH was 12.5 mg. per rabbit, and it was necessary to inject the material 2 hr. prior to the intravenous or "provocative" injection in order to bring about inhibition; when the same amount of ACTH was given 2 hr. prior to the preparative intradermal injection, no inhibition of the phenomenon occurred. The results with cortisone indicated that relatively enormous amounts of this substance were necessary in order to bring about inhibition, and in no instance was inhibition produced in all animals tested. In fact the authors have stated that no significant inhibition was observed when 40 mg of cortisone were injected intramuscularly 2 hr. before the intravenous injection of toxin, only partial inhibition resulted from the injection of 75 mg. at this time, and 60 mg. injected 4 hr. before the intravenous injection failed to inhibit. With material as insoluble and slowly absorbed as cortisone, one would expect a greater biological effect after 4 hr. than at 2 hr, yet the contrary was observed. The possibility that some of the effects attributed to cortisone may have been due to the suspending agents employed in commercial cortisone preparations was not excluded in the data presented

Results which were not in agreement with the foregoing were obtained in experiments utilizing saline suspensions of crystalline cortisone by Thomas & Mogabgab (46) and Thomas & Good (47, 53) Rabbits were treated with 12 mg of cortisone per kg. for four days, with preparation of the skin by bacterial toxin on the third day and intravenous injection of toxin on the fourth. An untreated group of rabbits was prepared and challenged with the same doses of bacterial toxin. In nine of the 10 animals in each group, typical Shwartzman reactions were elicited, indicating that under conditions of prolonged and excessive dosage with cortisone the Shwartzman phenomenon was not inhibited. During the course of these experiments it was noted that many of the prepared skin areas were markedly different in appearance from those in control untreated rabbits. During the first 12 hr after the intradermal injection of toxin no local reactions were visible, while in the controls erythema and edema appeared at the site of injection within 4 hr. After 18 to 20 hr. there was still no edema in the treated rabbits, but many small petechiae were noted within an area of skin equivalent in size to the inflamed area in the controls When the intravenous injection of toxin was withheld, it was observed that these petechiae increased in size and density until, at about 30 hr. after preparation, the gross appearance of the skin was comparable to that of a mild but definite Shwartzman reaction. Histological examination of this tissue revealed widespread thrombosis of the small vessels in the subcutaneous tissue, a moderate degree of inflammatory reaction with an exudate chiefly composed of polymorphonuclear leukocytes,

Hypersensitivity reactions.—The inhibition of various types of experimental hypersensitivity in animals by cortisone and ACTH has been well demonstrated by several groups of workers (59, 60, 61). Germuth *et al* (59) showed that the Arthus reaction in rabbits sensitized by repeated injections of crystalline egg albumin was markedly inhibited by treatemnt with either hormone, and the inhibitory effect was correlated with the diminution of circulating antibody They found that the passive Arthus reaction, produced by the administration of antibody to normal animals, was in no way affected by cortisone or ACTH, nor were the levels of transferred antibody altered by treatment. The latter observation is supporting evidence for the view that the effect of cortisone and ACTH on hypersensitivity reactions is mediated through the inhibition of antibody production rather than by an effect on the reaction of tissues to antigen-antibody combinations

Rich, Berthrong and their co-workers (62, 63), Seifter (64), and Wedgewood *et al* (65) have shown that experimental serum disease in rabbits, produced by massive intravenous injections of foreign serum and characterized by inflammatory lesions in the kidneys, heart, and blood vessels, is inhibited or prevented by treatment with cortisone or ACTH Rich (62) reported that ACTH provided protection against both the myocardial and renal lesions of serum disease, while cortisone prevented the cardiac lesions but appeared to bring about more extensive glomerular lesions than were seen in untreated control rabbits. The latter observation is without explanation, but may be related to the phenomenon of bilateral cortical necrosis in cortisone-treated rabbits (47), described in a preceding section. The relationship between the therapeutic effects of cortisone and ACTH in serum disease and the levels of circulating antibody has not been sufficiently clarified Two groups of workers (62, 75) were unable to demonstrate sufficient alterations in antibody level to account for the prevention of lesions; Germuth (59), however, has criticized the validity of the methods employed for quantitative antibody estimation

Numerous and somewhat conflicting reports have appeared concerning the effects of cortisone and ACTH on other types of hypersensitivity reactions in experimental animals The weight of evidence favors the view that the anaphylaxis and histamine shock in the guinea pig are not affected (66) The tuberculin reaction may be quantitatively reduced in intensity under the influence of prolonged treatment but is not qualitatively altered (67, 68) Long, Miles & Perry (69) state that the desensitizing effect of cortisone and ACTH on the tuberculin reaction in guinea pigs may be abolished by propylthiouracil, while the degree of desensitization is greater in animals treated with thyroxine This interesting observation is without explanation at the present time, the authors suggest that ascorbic acid metabolism may be involved in the effect

Nephrotoxic nephritis produced by the passive transfer of antikidney sera is not prevented by cortisone or ACTH (70, 71). Kabat *et al.* (72) and Moyer *et al* (73) have shown that allergic encephalomyelitis resulting

small extent; one result of this is that it is not possible to produce the Shwartzman reaction in normal rabbits when the provocative injection is made into the skin instead of by vein. The occurrence of renal necrosis following an intradermal injection of toxin suggests that one effect of cortisone may be to interfere with the capacity of skin tissue to hold toxin at the injected site and prevent its appearance in the blood.

The Effect of Cortisone on Bacterial Immunity and Hypersensitivity in Animals

The formation of antibody.—The older literature dealing with the role of the adrenal cortex in immunity and antibody formation contains numerous references to the adrenal gland as a key organ in immunity (54). In part, this assumption was based on the extreme susceptibility to infection of patients with Addison's disease as well as adrenalectomized animals. Definitive evidence is lacking, however, for the direct participation of the adrenals in this function. Eisen and co-workers (55) showed that adrenalectomized animals were capable of producing appreciable levels of antibody. According to White (52), cortisone and ACTH have a stimulating effect on antibody production which is associated with an increase in the number and activity of phagocytic cells in lymphoid tissue and the dissolution of antibody-containing lymphocytes The anamnestic immune response was attributed to the latter mechanism by Dougherty, Chase & White (56), who reported that the administration of ACTH was followed by a rise in circulating antibody. Subsequent studies by other investigators (57, 58, 59) employing quantitative immunochemical techniques failed to confirm this observation. Recently, substantial evidence has been obtained to indicate that if cortisone and ACTH produce any change in the level or rate of production of antibody, the effect is one of inhibition rather than stimulation. Bjorneboe, Fischel & Stoerck (58) studied the effect of cortisone and ACTH on the concentration of antipneumococcal antibody in rabbits. Both substances were found to cause a sharp reduction in antibody formation below that observed in untreated controls. Moreover, when animals were treated after immunization was well advanced, the level of already circulating antibody was reduced The authors suggested that the diminution in antibody content may have been due to the negative nitrogen equilibrium caused by the hormones, with actual destruction of antibody protein, and in part to inhibition of the synthesis of antibody resulting from a decrease in the number of mononuclear cells in lymphoid tissue. Similar observations were made by Germuth, Oyama & Ottinger (59) These workers tested the formation of antibody against crystalline egg albumin in rabbits during treatment with cortisone in a dosage of 2 mg per kg each day. When treatment was started at the time of immunization antibody formation was markedly suppressed, and when cortisone was administered following sensitization there was a rapid decline in circulating antibody. A similar effect was produced by ACTH, although the degree of antibody inhibition was much less marked.

relative susceptibility of various animal species to the effects of the hormones. On the other hand, the results would warrant an attitude of caution in the use of the material even if no information were available concerning their effects in human infections. As it is, there is some information, largely of a preliminary nature, which will be summarized below; it is not enough to settle the problem but serves to indicate that the problem exists.

Tuberculosis.—Initial reports on the results of treatment of tuberculosis with ACTH and cortisone described the prompt and spectacular relief of many of the subjective symptoms of the disease, accompanied by remission of fever, unusual sensations of well-being, and increase in appetite. These changes were observed by Freeman and co-workers (78) in two patients, but it was also noted that spread of the infection occurred in one. LeMaistre *et al.* (79) described rapid improvement in the gross appearance of the local lesions in laryngeal tuberculosis during ACTH treatment, but noted that exacerbations occurred after treatment was stopped. The latter authors also reported the continuing advance of systemic tuberculosis infections despite apparent relief of symptoms.

Recently, several reports have appeared which indicate quite clearly that tuberculosis is not only adversely affected by cortisone or ACTH but may be activated from the latent state. King *et al.* (80) reported the case of a 39-year-old woman with incapacitating rheumatoid arthritis who received treatment with cortisone over a period of seven months, at the end of which time she was found to have x-ray evidence of pneumonitis at the right lung base. Cortisone therapy was stopped. One month later both lungs showed extensive involvement which was roentgenologically interpreted as "acute caseous tuberculosis of the type seen in the aged, terminal uremics, diabetics, or in the very young." Her course was rapidly down hill and she died within six weeks after the detection of pulmonary involvement.

Popp and co-workers (81) described the case of a 64-year-old woman with rheumatoid arthritis, known to have had inactive pulmonary tuberculosis for approximately three years, who received cortisone in two separate courses of one month each in a dosage of 100 mg every one or two days. At the end of the second course an hemoptysis occurred and cortisone was discontinued X-ray at this time showed extension of pulmonary lesions and sputum examinations revealed tubercle bacilli, the first positive sputum in more than three years The authors concluded that reactivation of the infection had been brought about by cortisone

Fred *et al.* (82) described a 50-year-old man with chronic rheumatoid arthritis, in whom no evidence of pulmonary tuberculosis was demonstrable by x-ray during a 10-week period prior to treatment, who received ACTH in a daily dosage of 20 mg. for approximately one month. The symptoms of arthritis were relieved, but five weeks after beginning ACTH he developed a spiking temperature and x-ray evidence of pneumonia. At this time 100 mg. of cortisone daily was added to his treatment. One month later he died

from autoimmunization with brain extracts and adjuvant mixtures may be prevented if treatment is begun at the time of antigen injection; their results indicate that the effect is probably due to suppression of the cellular reaction at the site of antigen deposition rather than any direct action on the cerebral lesions.

The demonstrated inhibition of antibody formation might be regarded as one plausible mechanism for the enhancement of bacterial and virus infections by cortisone and ACTH. There is, however, substantial experimental evidence to the contrary. In most instances, overwhelming infection occurs within too short a time to involve an effect on antibody formation (16, 18, 21, 32, 36). There is no demonstrable antibody mechanism in the chick embryo to account for the increased susceptibility to virus infection (34). Moreover, immunized rabbits are much less susceptible to cortisone-induced streptococcal infection than nonimmunized animals (22), indicating that cortisone does not, in this instance, interfere with the protection provided by antibody.

Effect on hyaluronidase.—Menkin (74) demonstrated that the increased permeability of vessels in inflamed tissues is reduced by adrenal cortical extract. The possibility has been suggested that some of the effects of cortisone and ACTH may be mediated through an inhibitory action on hyaluronidase, presumably by limiting the spread of infectious agents or their products. Seifter (75) presented experimental evidence for interference with membrane permeability by several steroid compounds. Benditt and coworkers (76) showed that the generalized increase in capillary permeability caused by intravenously administered testicular extract could be prevented by pretreatment with cortisone or ACTH. Subsequently, the latter workers (77) demonstrated that hyaluronidase and the permeability-enhancing factor in testis extract are not identical substances as had previously been assumed. From this it would appear that cortisone and ACTH have an inhibitory effect on two separate tissue properties, one which depolymerizes hyaluronic acid and another which augments permeability. Whether either of these properties is concerned with defense against the systemic dissemination of infectious agents remains to be determined.

The Effects of Cortisone and Adrenocorticotropic Hormone on Infectious Disease in Human Beings

The preceding portion of this review has been concerned largely with animal investigations which provide experimental evidence for the enhancing effect of cortisone and ACTH on various types of infection. In considering the possible application of such observations to the problem of human therapy, it should be pointed out at the outset that the dosages of hormone employed in most of the animal experiments are greatly in excess of any conceivable therapeutic regime in clinical medicine. Therefore, any conclusions as to the hazards involved which are based directly on animal studies would be unwarranted until more information is available concerning the

cortisone or ACTH, in which it seemed clear that enhancement of infection occurred.

Fungus infections.—Sutliff & Norman (30) described the results of treatment with ACTH of North American blastomycosis. A marked increase was observed in the degree of inflammation and necrosis in the lesions, accompanied by severe local pain. Although the degree of tissue damage appeared to be aggravated during treatment, spread of the infection to other areas was not noted. Shulman (87) reported a case of fatal moniliasis in an anemic child during treatment with ACTH

Malaria.—Kass, Geiman & Finland (88), in the course of investigations of the antipyretic action of ACTH (39), carried out studies in three patients with induced benign tertian malaria Control observations were made in seven patients infected with the same strain of *Plasmodium vivax* who did not receive ACTH. After the third paroxysm ACTH was given intramuscularly every 6 hr. throughout the course of two or three succeeding paroxysms; during this time no other therapy was administered. The duration of fever in each paroxysm was found to be slightly less in the ACTH treated patients, but the actual temperature achieved was not appreciably lowered The most striking effect was that the number of malaria parasites was significantly greater in the blood of the ACTH treated patients than in the control group. Except for transient psychotic manifestations in one of the treated patients, no untoward reactions occurred; after the third paroxysm the disease was terminated by appropriate antimalarial treatment in each case. It should be noted that these authors have also observed the enhancement by ACTH of malarial infection in monkeys, with the production of experimental black water fever (89)

Other infections—Several investigators have commented on the occurrence of spontaneous systemic infections during the course of treatment of various conditions with ACTH or cortisone (3, 82, 90, 91) Although no comprehensive study of such infections has yet appeared, certain observations are worthy of note Fred *et al* (82) reported the development of diffuse purulent meningitis in a patient under treatment for multiple myeloma, and acute disseminated actinomycosis in a patient with acute lymphatic leukemia Bunim (92) reported a case of fatal pneumococcal septicemia in which ACTH had been used for the treatment of arthritis Dubois-Ferriere (93) reported the occurrence of an extensive gluteal abscess due to *Staphylococcus aureus* in a patient who had received 100 mg. of cortisone daily for four months An interesting feature in this case was the complete absence of signs of inflammatory reaction in the involved tissue, the abscess was accidentally detected when a needle was inserted for an intramuscular injection

Other investigators have undertaken the deliberate treatment of certain types of infection with ACTH or cortisone in order to obtain well-controlled data Hahn and his co-workers (94) administered cortisone to 87 patients with acute streptococcal tonsillitis and pharyngitis, in a daily dosage of 50 to 100 mg over a period of six to ten days after the onset of infection. At the

with bilateral caseo-cavernous tuberculosis and confluent tuberculous pneumonia. The latter authors mention, without details, another patient treated for dermatitis who developed miliary tuberculosis

In a recent symposium on the chemotherapy of tuberculosis (83), approximately 20 cases of clinical tuberculosis were reported in which the end results were unfavorable. The accumulated evidence, both from experimental animals and observations on human beings, was considered sufficiently pointed to elicit the following recommendation by the National Tuberculosis Association (84):

Because the actions of ACTH and cortisone upon factors of resistance to tuberculosis have been shown to be *deleterious in these three species of experimental animals* (mice, guinea pigs, and rabbits), and there is strongly suggestive evidence along the same lines in human beings, it is recommended that these substances not be used in patients with active tuberculosis, and that they be used with extreme caution even in human beings with possibly latent tuberculosis infection, until such time as further investigative work has shown that such administration may be safe. The routine diagnostic examination for tuberculosis of patients under physicians care is especially necessary for patients who are being considered for ACTH or cortisone therapy.

Pneumonia —Reference was made earlier to the studies of Finland, Kass & Ingbar (5, 85, 86) concerning the effects of ACTH in pneumococcal and primary atypical pneumonia. These authors carried out detailed clinical, bacteriological and serological studies in three cases of pneumococcal pneumonia and two of atypical pneumonia. Their results were summarized as follows (85)

Three patients with pneumonia due to types 8, 2, and 1 pneumococci, respectively, and two with primary atypical pneumonia were treated with pituitary adrenocorticotropic hormone Defervescence of fever and relief from symptoms and signs of toxemia occurred promptly in all cases In three instances the patients remained asymptomatic and afebrile, despite the persistence of bacteremia in one and the continued production of rusty sputum in another One patient with pneumococcal pneumonia experienced an exacerbation of symptoms while receiving ACTH with remission when the dose was increased This patient had an extension of his pulmonary lesion and later developed empyema One patient with viral pneumonia had a similar exacerbation of symptoms while receiving the hormone, with prompt relief from all symptoms except cough when the dose of ACTH was increased but with return of fever and malaise after ACTH was withdrawn No evidence was obtained of any bactericidal action exerted by adrenal steroids Anti-pneumococcal antibodies and cold agglutinins appeared at the anticipated time, with no evidence of acceleration or delay in their production . *It is concluded that ACTH may in some instances* induce profound changes in the clinical symptoms of patients with acute infections without demonstrably effecting the etiologic agent There was no evidence from these cases of any effect on the production of specific antibodies

The results indicated that the clinical evidences of damage by the injecting agents were suppressed during treatment, but the important question whether the extent of infection was actually made worse was not settled by the data. Other workers (91, 92) have since reported instances of fatal pneumococcal pneumonia and septicemia during the administration of

tion of specific antibody in human beings following injections of pneumococcal polysaccharide antigens. On the other hand, Long & Favour (105) observed alterations in the delayed type of bacterial hypersensitivity reactions in the skin of 34 patients during treatment with ACTH or cortisone. These authors tested the dermal reaction to tuberculin and to an antigen prepared from group A hemolytic streptococci and observed that the reactions were either completely obliterated or reduced in intensity during hormone therapy. Within 7 to 28 days after treatment the dermal reactions had returned to their previous degree of activity.

SUMMARY

The capacity of cortisone and ACTH to bring about enhancement of infection in experimental animals is sufficiently well established by the evidence to warrant the listing of this as one of the more important properties of these hormones. That the property is entirely nonspecific, in the bacteriological sense, is indicated by the wide variety of unrelated microorganisms and viruses with which enhanced infection may be produced. These include tubercle bacilli, pneumococci, treponemes, brucellae, typhoid bacilli, *streptococci, fungi, malarial parasites, trypanosomes, poliomyelitis,* mumps, influenza A and B viruses, and Coxsackie virus. The effect is not confined to living microorganisms, since it has been shown that a necrotizing type of tissue damage occurs in hormone-treated animals with bacterial toxins which provoke reversible inflammatory reactions in untreated animals.

The degree to which these observations have bearing on the problem of human therapy remains to be settled. At the present time there is evidence that certain types of human infections may be aggravated by ACTH or cortisone. These include tuberculosis, malaria, and perhaps pneumococcal infection and blastomycosis. There are reports of spontaneous infections occurring during the treatment of various conditions with cortisone or ACTH; included among such infections are reactivated tuberculosis, pneumococcal septicemia, staphylococcus infection, noniliasis, and actinomycosis. On the other hand, untoward effects did not occur when cortisone or ACTH were employed in the treatment of other types of infection, including hemolytic streptococcal infections, typhoid fever, virus hepatitis, and poliomyelitis. Proper evaluation of the degree of hazard to human beings will require detailed bacteriological investigations in many treated patients It has been emphasized (3, 90, 91) that the clinical manifestations of infection are greatly altered by hormone treatment, and reliance on the accepted criteria for diagnosis may result in the overlooking of severe and extensive infections. As examples, pneumococcal pneumonia and septicemia, purulent pericarditis, peritonitis, and staphylococcal abscess and septicemia have occurred without recognition in treated patients (91, 92, 93).

Many mechanisms have been proposed to account for the effects observed on infection. The demonstrated depression of antibody levels and the inhibition of formation of new antibody offer a possible explanation, but

same time a group of 87 other individuals involved in the same epidemic of streptococcal infection were observed as controls. Cortisone exerted no effect on the symptoms or physical signs of the infection. There were no significant differences between the untreated and treated groups in the occurrence of suppurative complications of streptococcal infection, nor in the incidence of subsequent rheumatic fever. Abnormal electrocardiograms were encountered in an equal number of patients in the two groups. The increase in the antistreptolysin titer following infection was somewhat less in the sera of the treated group than in the control patients one week after the onset of infection, but at two, three, and four weeks the titers of antibody were higher in the patients who had received cortisone. It was also noted that the cortisone-treated patients exhibited fever for a longer period of time than the control patients.

Smadel (6) and Woodward (7) and their co-workers reported the use of cortisone in patients with typhoid fever, with apparently favorable results. The symptoms and signs of severe intoxication were greatly ameliorated by cortisone, and when given in conjunction with chloramphenicol the disease was relatively mild and of short duration. Cortisone exerted no effect on the viability of typhoid bacilli so far as could be determined by cultures of blood and stools. On the other hand, no adverse effects and no evidence of enhancement of the infection were noted.

Colbert *et al.* (95) employed ACTH in the treatment of considerable number of patients with acute viral hepatitis, with results which were interpreted as beneficial. The patients were not only relieved of malaise and anorexia, but a prompt fall in serum bilirubin was observed which seemed to be the result of ACTH treatment. In no instance were signs of increased hepatic damage observed. A long term follow-up study of these cases would be of extreme importance

Coriell *et al* (96) employed ACTH in the treatment of acute poliomyelitis during the course of an epidemic in 1949. Comparison of the outcome in treated patients with the course in a comparable group of untreated controls revealed no evidence of any effect on the course or outcome of the disease.

Hypersensitivity and immunity in man.—Numerous clinical reports from many centers in the past several years have conclusively established the value of ACTH and cortisone in the treatment of various human ailments which are commonly accepted to be based on hypersensitivity. These include asthma, hayfever, and drug sensitivity (97, 98, 99). They have also been shown to have remarkable therapeutic effects, although not proven to be curative, in certain idiopathic diseases in which hypersensitivity is suspected to play a role, such as rheumatic fever (100), rheumatoid arthritis (4), lupus erythematosis (101), periarteritis nodosa (102), and dermatomyositis (103).

The actual effect of these materials on antibody production and hypersensitivity reactions in man remains to be evaluated. Mirick (104) has presented evidence which indicates that they exert no effect on the produc-

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in most of the animal experiments cited the enhancing effect occurred too early in the course of infection to implicate this mechanism Some writers have suggested that the effect may be due to an impairment of the inflammatory reaction (91, 106, 107), but little is known of the actual role of this reaction or its participants in defense against infection. The available information concerning the effect on phagocytosis does not clarify the problem Selye (108) reported that the phagocytosis of india ink particles is increased in ACTH-treated animals, and Dougherty & White (109) showed that the number and activity of phagocytic mononuclear cells in lymphoid tissues becomes increased as the result of adrenal cortical stimulation. However, it is conceivable that the depletion of lymphocytes caused by cortisone or ACTH may reduce a reservoir of potential macrophages (110) with impairment of the defense mechanism in injured or invaded tissues; experimental evidence on this point is not yet available. Crepea, Magnin & Seastone (111) reported that the phagocytosis of pneumococci by polymorphonuclear leukocytes from human beings was depressed to a moderate degree during treatment with cortisone or ACTH in 9 of 10 subjects studied. It is questionable whether the degree of depression was sufficient to account for any major change in general resistance to infection

Various "acute-phase" constituents of blood which appear early in the course of many infections are reduced in level during hormone treatment; these include the nonspecific inhibitor of hyaluronidase (112, 113), serum mucoproteins (114), and C-reactive protein (115) Although no known function can be assigned to any of these substances, it is possible that an analogous blood constituent, as yet unrecognized, may be important in resistance to infection. If a single mechanism is involved it must be extremely versatile, since it involves protection against bacteria, viruses, protozoans, fungi, and bacterial toxins By further experimental studies of cortisone and ACTH, it should be possible to enrich greatly our understanding of the process of infection.

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DISEASES OF THE GASTROINTESTINAL TRACT

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The previous two reviews of this field have been admirable in the manner in which almost all of the important topics within the entire specialty were covered and brought up to date. The present review attempts no such goal. Within this broad field, specific subjects are selected in which significant advances have been made within the past year, which had not been completely covered in the preceding reviews, and which are of particular interest to the reviewer. Particular attention is given papers published between September 1950 and September 1951.

ADRENOCORTICOTROPIC HORMONE AND CORTISONE IN GASTROINTESTINAL DISEASE

Adrenocorticotropic hormone (ACTH) and cortisone have been shown to have a remarkable effect upon the function of certain areas of the gastrointestinal tract: glycogen stores in the liver are increased; serum amylase levels may be depressed; production of hydrochloric acid, pepsin, and soluble mucus fractions by gastric mucosa are augmented; and small intestinal absorption may be improved.

These hormones have already been explored therapeutically in many gastrointestinal diseases Effects observed have ranged from that of definite harm (peptic ulcer) to that of striking temporary effectiveness (acute idiopathic ulcerative colitis). In no gastrointestinal disease have the results been uniformly satisfactory.

Viral hepatitis.—ACTH and cortisone commonly produce a marked improvement in appetite and sense of well-being in viral hepatitis Voluntary caloric intake usually increases dramatically. Published clinical observations [Thorn *et al.* (1), Colbert *et al.* (2), and Sborov *et al.* (3)] have varied widely regarding the effect of these steroids upon the hepatitis. In a few cases, it is believed that there resulted prompt defervescence of the disease with rapid loss of jaundice. In most cases, no obvious change in the clinical status of the patient occurred.

Chronic liver disease.—In chronic liver disease appetite stimulation is also impressive, even in advanced disease states Fluid retention is a marked hazard unless drastic sodium restriction is used Pruritus may disappear in some patients. In most clinical reports, no striking improvement in the disease itself has occurred which can be specifically attributed to the hormonal agents Published records have thus far come from Bluemle *et al.* (4) Butt and co-workers (5), Gyorgy & Bluemle (6), Bongiovanni & Eisenmenger (7), Brown (8), and Hangar & Collins (9).

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higher dosage scale. Reports reviewed are those by Dutoit & Bauer (26), Dearing & Brown (27), Gray *et al.* (21, 22, 28) Machella & Hollan (19), Redish (18), Rossmiller *et al.* (29), Elliott *et al.* (30), Kirsner & Palmer (25), Kirsner (31), and Halsted *et al.* (32). The most extensive report, dealing with experiences in 45 patients, is that of Kirsner & Palmer (25).

PEPTIC ULCERATION

Two very important monographs of peptic ulcer have been published during the past year. The book by Ivy, Grossman & Bachrach (33) attempts a complete review of the history and accumulated knowledge of all phases of the subject and is particularly excellent for the assembling of important experimental data. The second book, compiled by 77 leading members of the American Gastroenterological Association under the able editorship of Sandweiss (34), while having the same general goals, particularly develops recent important clinical and surgical observations and is therefore somewhat more useful to clinicians.

Etiologic Factors of Peptic Ulceration

The vascular influences upon the continuance of chronic gastric ulcer have been re-examined by British investigators employing injection techniques and microradiographs. Arteriovenous shunts in the stomach wall capable of diverting blood from the mucosa to the submucosa have been demonstrated [Barclay & Bentley (35, 36); Doran (37), Barlow (38)]. Arterial anastomoses are normally so numerous as to make necessary a rather extensive vascular block to result in mucosal ischemia [Key (39)]. The suggestion is made [Barclay & Bentley (35, 36)] that arteriovenous shunts are under the control of the autonomic nervous system, which is capable, upon proper stimulation, of rendering large areas of the gastric mucosa ischemic by the opening of principal shunting vessels. Key has demonstrated wide-spread vascular occlusion, extending deep into the stomach wall, in the base of chronic gastric ulcers. In acute ulcers, in contrast, there appears to be a hyperemia, possibly with marked venous stasis. The commonest site of gastric ulcer, the lesser curvature, has a diminished vascular density [Doran (37)].

The existence of gastrin, the hormonal stimulus for gastric secretion which is produced by the gastric antrum, is proven by the important work of Grossman *et al.* (40) and of Dragstedt and co-workers (41, 42). Mechanical stimulation of nerve-severed, transplanted antrum yields increased acid-pepsin secretion from the remaining stomach, even though the latter may have been vagally denervated Regular development of gastric and stomal ulcers in experimental animals when the antrum of the stomach is transplanted to the colon is reported [Dragstedt *et al* (42)]. This work provides the much-needed explanation for the previous recognition by surgeons of the importance of complete removal of the antral mucosa during subtotal gastrectomy for duodenal ulcer

The adrenal phase of gastric secretion has been demonstrated by Gray

Peptic ulcer.—In view of the well-demonstrated adrenal phase of gastric secretion with augmented production of hydrochloric acid and pepsin [Gray *et al.* (10) and Spiro *et al.* (11)], one would expect exacerbations of peptic ulcer disease under ACTH and cortisone therapy. This is certainly one gastrointestinal disease in which the use of these agents is uniformly harmful and dangerous. Reports of hemorrhage and perforation of previously well-controlled peptic ulcers have appeared [Habif *et al.* (12); Kuzell & Schaffarzick (13); Hollander (14)].

Acute pancreatitis.—Hume & Moore (15) conclude from brief experience that adrenal hormones are of value in treating the shock of severe hemorrhagic pancreatitis. Mild forms of the disease continued to improve after addition of hormonal therapy, and severe cases sometimes continued progressively downhill in spite of administration of ACTH. The almost uniform depression of serum amylase level was striking.

Idiopathic steatorrhea.—Cortisone has been shown to induce a very satisfactory remission in nontropical sprue [Taylor and associates (16)]. An increase in small bowel fat and nitrogen absorption with a corresponding improvement in many other features of the disease syndrome is reported. Similar impressive findings in these patients treated with ACTH have been observed by Jones, Ellis & Point (17).

Regional enteritis.—Experiences with adrenal hormone therapy in this disease have been widely variable. After a survey of the reports, one has the impression that striking improvement may sometimes occur if the disease is of rather short duration and in an acute phase, whereas no benefit is likely to result if an advanced chronically cicatrized phase exists [Redish (18); Machella & Hollan (19); Astwood *et al.* (20); Gray *et al.* (21, 22); Stanley *et al.* (23)]

Idiopathic ulcerative colitis.—Of all gastrointestinal disease, ulcerative colitis has been given the most extensive trial on ACTH. Results have been widely variable. One concludes that temporary arrest of the acute disease may occur and be most dramatic. Whereas the total eventual improvement of the patient may be no greater than with previous medical regimens, the speed with which remission may be attained is frequently much accelerated. Stool output of fluid and blood, sedimentation rate, and fecal lysozyme titer improve in parallel fashion. Because relapses after cessation of therapy are not unusual, it has become quite obvious that ACTH and cortisone treatment at best produces an arrest and not a cure of the disease. Particular hope is had for their effective use in the fulminant variety of idiopathic ulcerative colitis. An unusual frequency of marked lower bowel hemorrhage during ACTH therapy has been experienced [Jones & Ellis (24)]. Acute disease in the early stage appears to respond far better than does the advanced chronic cicatrized stage Complete therapeutic failures are sometimes observed. Difficulties have been experienced in adjusting dosage to the effective level for a given individual; one wonders if the disappointments with cortisone [such as that of Kirsner *et al.* (25)] might have been avoided with a

that a dose of at least 2 Gm. of powdered resin is required to elevate gastric pH consistently. Similarly, Wirts and Rehfuss (55) used a dose of 3.2 Gm. of resin and achieved a gastric antacid effect comparable to that of 0.6 Gm. of a modified Sippy powder or aluminum hydroxide.

Clinical observations thus far reported indicate that anion exchange resins are definitely helpful in the treatment of patients with ulcer disease. Interestingly enough, beneficial results have been obtained with doses probably too small to have produced an adequate or consistent decrease in gastric acidity.[1] Pain relief is rapid in most cases, and ulcer craters tend to heal rapidly. Recurrences take place, however, and complications may develop while the resin is being taken.

Theoretically, anion exchange resins would appear to be meritorious drugs well adapted for use in ulcer management. Continuing efforts to reduce particle size and improve quality may eventually result in a product much more effective clinically than those now at hand seem to be.

Radiation therapy.—Experiences with radiation therapy in peptic ulcer are reviewed by Ricketts *et al.* (56), Palmer *et al.* (57), and Ricketts & Palmer (58). This group considers radiation therapy to be a useful adjunct in the medical management of certain ulcer patients. The purpose of the radiation is to suppress gastric secretion. The duration of effect and degree of suppression obtained is said to be variable and unpredictable. All phases of gastric secretion are diminished as the result of direct cellular injury. Irradiation gastritis commonly results but is generally asymptomatic. These authors sum up their experience as follows [Ricketts & Palmer (58)].

It is of interest to contrast the mechanism of action of radiation therapy and vagotomy: radiation acts directly on the secretory cells; vagotomy abolishes the cephalic phase of gastric secretion. In a sense the indications for the two procedures are opposite, vagotomy is most effective in jejunal ulcer and duodenal ulcer, less so in gastric ulcer, whereas radiation therapy has given perhaps the majority of its most dramatic results in gastric ulcer. The explanation is to be found in the effect of these procedures on gastric secretion. A satisfactory vagotomy gives an effective and permanent reduction of the hypersecretion present in duodenal ulcer; radiation therapy may produce such an effect, but is less likely to do so in such patients than it is in those with gastric ulcer and a low grade secretion. Nevertheless, radiation therapy as described has seemed to us to be definitely worth while, especially as an adjunct in the medical management of the refractory peptic ulcer.

Hormonal therapy.—The generally conceded, quite unsatisfactory state of hormone therapy for peptic ulcer is ably summarized by Sandweiss (59). Further conclusive reports of the complete noneffectiveness of present-day enterogastrone preparations are given by Bone and associates (60), by Wollum & Pollard (61), and by Gambill *et al.* (62).

Surgical Treatment of Peptic Ulcer

Esophageal ulcer.—Benedict (63) states that operation is rarely indicated for benign peptic ulcer of the esophagus unless there occurs massive hemor-

[1] The reviewer suspects that this may be the result of the well-known effect of placebo upon ulcer patients.

and co-workers (10). Administration of ACTH or cortisone produces an increase in secretion of hydrochloric acid and pepsin. The latter is reflected by an increased excretion of uropepsin [Spiro *et al.* (11)].

Medical Treatment of Peptic Ulcer

Banthine.—Further reports have appeared relating favorable experiences with methantheline bromide (Banthine; β-diethylaminoethylxanthene-9-carboxylate methobromide) as an effective adjunct in the medical management of duodenal ulcer [Poth & Fromm (43); Plummer and co-workers (44); Brown & Collins (45)] The promptness of pain relief in the majority of patients has been striking, suggesting to some the result of a direct blockade of afferent visceral pain fibers [Asher (46)]. The extreme enthusiasm and faith in this drug alone, presented by the previous reviewers [Grimson & Flowe (47)], is taken with justifiable skepticism by McHardy (48). Although effective anticholinergic suppression of gastric secretion has been repeatedly demonstrated by various workers [Grimson & Flowe (47); Smith *et al.* (49); Benjamin *et al.* (50)], the loosely-used phrase "complete medical vagotomy from Banthine" is invalid; for example, the gastric secretory response to insulin hypoglycemia in man is not abolished even by toxic doses of the drug [Smith *et al.* (49); Plummer *et al.* (51)] Smith and co-workers (49) report that methantheline bromide produces a marked reduction in nocturnal gastric secretion of peptic ulcer patients in doses which do not give "intolerable side effects" It will be difficult to determine whether methantheline bromide really, as alleged by many, can give in duodenal ulcer patients a satisfactory suppression of gastric secretion with less side reaction than is produced by atropine. One wonders if the effect of methantheline bromide upon the gastric secretion of duodenal ulcer patients will eventually be found to be as variable and unpredictable as demonstrated for atropine [Levin and co-workers (52)]

Anion exchange resins.—Berk (53) has summarized admirably the published experiences with anion exchange resins as antacids, as follows:

> Anion exchange resins are insoluble and inert plastic substances capable of removing acids from solutions and releasing them in an alkaline medium with restoration of the resin to its original state The speed and degree of acid neutralization depend upon the contact time and the particle size of the resin The substances have been demonstrated to neutralize effectively the acidity of hydrochloric acid solutions and gastric juice *in vitro*, and gastric and duodenal bulb acidity *in vivo*. Pepsin is adsorbed and peptic acidity markedly reduced. Acid-base balance is not disturbed No acid rebound has been observed, nor does the urinary tract become alkalinized. Save for occasional diarrhea, gastrointestinal motility and bowel habit are not altered. Side reactions are minimal, but nausea, vomiting and fullness have been noted after large doses Observations in rats, dogs and man have failed to disclose toxic changes
>
> The material is available in capsules, tablets, powders ("Resinat," "Exorbin").

omy has been incomplete or has been performed with an enteroenterostomy which diverts the alkaline duodenal secretions away from the gastroenterostomy stoma [Dragstedt & Woodward (72)].

Duodenal ulcer.—Walters & Belding (76) feel that vagotomy alone has little place in the management of duodenal ulcer, and prefer two-thirds gastric resection. The experience of Glenn (71) leads him to the same opinion. Occasionally, simple gastrojejunostomy is still employed in older age, poor-risk patients with good results.

Dragstedt & Woodward (72) have decided that vagotomy combined with gastroenterostomy of small size should replace subtotal gastrectomy for duodenal ulcer. Palmer, Kirsner & Levin (69) support this contention. Farmer *et al.* (77) report that acid secretion in duodenal ulcer patients who have had vagotomy plus posterior gastroenterostomy is often within the range of those who develop gastrojejunal ulcer following posterior gastroenterostomy in subtotal gastrectomy. In their hands, resection of 50 per cent of the stomach plus vagotomy or subtotal resection alone has reduced gastric acidity more than vagotomy plus posterior gastroenterostomy. According to these authors, short term follow-up studies suggest that clinical results from 50 per cent gastric resection plus vagotomy are equal or superior to more radical gastric resection with or without vagotomy. Jordan (75) reports the Vagotomy Study Committee's statistics to show that the addition of vagotomy to gastric resection has not improved subjective or objective results in duodenal ulcer and that subtotal gastric resection alone or with vagotomy has produced better results in the control of peptic ulcer than gastroenterostomy plus vagotomy

Sequellae of Gastric Resection

Types of undesirable physiologic disturbances occurring as a result of gastric resection are reviewed by Wells & Welbourn (78), Brain & Stammers (79), and Capper & Butler (80) Before, these have loosely been lumped under the heading "dumping syndrome," but comprise a variety of disturbances. A worthwhile attempt to organize these according to mechanism has been made by Wells & Welbourn (78). Billroth II types of anastomoses (gastrojejunostomy) are chiefly considered. The four major results of gastric resection likely to produce symptoms have been listed as (*a*) rapid emptying of the gastric remnant, (*b*) stasis and reflux from stomach or afferent loop, (*c*) reduction of gastric acid, and (*d*) removal of intrinsic factor. In addition, Capper & Butler (80) believe that many of the severe symptoms developing soon after ingestion of a meal are the result of traction upon the gastric remnant from the weight of the meal itself or from the weight of the afferent loop attached to the gastric remnant They suggest that reconstruction of the anatomical support for the stomach and anastomosis at the time of gastric resection might prevent much of the early postgastrectomy syndrome.

Rapid emptying of the stomach may produce distention of the jejunum, increase in peristaltic activity of intestinal tract, diarrhea, and alimentary

rhage, perforation, or progressive fibrosis with narrowing in spite of medical management and repeated bouginage; in the latter case, Benedict (64) suggests resection of the lower end of the esophagus. He had, however, earlier pointed out (65) the possibility that easy regurgitation of gastric juice into the lower esophagus following artificial esophagogastrostomy could lead to early recurrence. Wangensteen & Leven (66) have championed the theory of acid-pepsin regurgitation into the esophagus as etiologic in most instances of unexplained esophageal ulcer, esophagitis, and benign stricture of the esophagus; for this they advocate subtotal gastric resection to reduce gastric acidity. Cornell & Colp (67) similarly believe subtotal gastric resection indicated for peptic ulcer of the lower esophagus and report disappearance of esophageal ulcer in one patient by this means. Attention should be called to the fact that aberrant acid-pepsin producing gastric mucosa can occasionally be found in the lower esophagus in direct association with esophageal ulcer [Redish & Kertzner (68)]; it seems doubtful that subtotal gastric resection could cause disappearance of this variety of esophageal ulcer.

Gastric ulcer.—Because of the persistent problem of unsatisfactory differentiation between benign and malignant ulceration of the stomach, gastric ulcers are properly considered to be surgical problems primarily. Most internists and surgeons would agree with Palmer *et al.* (69), who state that subtotal gastrectomy continues to be the treatment of choice for gastric ulcer because (*a*) it removes the lesion which might be malignant and (*b*) the subsequent incidence of formation of jejunal ulcer is negligible. It has often been the claim of the internist that persistence and recurrence of benign gastric ulcer under medical management is far less common that for duodenal ulcer. Quite the contrary is the experience of Flood & Hennig (70) who followed carefully a large group of these patients; their recurrence rate was identical with that for duodenal ulcer.

Gastrojejunal ulcer.—Medical treatment of stomal ulceration is usually conceded to be ineffective. Vagotomy is considered preferable by Palmer & co-workers (69), who present for support recent statistics collected by the Vagotomy Study Committee of the American Gastroenterological Association. Similar views are expressed by Glenn (71), by Dragstedt & Woodward (72), and by Miller and associates (73). Crile & Brown (74) state:

> Since the results of vagotomy in the treatment of marginal ulcer are at least comparable to those following extensive gastric resection, its safety commends it as a standard treatment of marginal ulcer occurring either after gastric resection or gastroenterostomy.

Jordan (75), on the other hand, employs the statistics collected by the Vagotomy Study Committee of the American Gastroenterological Association to come to quite the opposite conclusion, that subtotal resection has produced better results than vagotomy alone! Occasional recurrence of gastrojejunal ulceration after vagotomy is recognized. This is especially likely to occur if a gastric resection has not been performed [Walters & Belding (76)] or if vagot-

not result in liver disease. Fatty cirrhosis in the United States nearly always occurs in alcoholics. The relation between alcohol and this type of liver disease is not clear but is thought to potentiate broad nutritional deficiency. Best *et al* (91) provide excellent evidence to indicate that the total caloric intake defines the amount of lipotropic agent (choline) necessary to prevent fatty infiltration of liver cells. Relative deficiency of lipotrope supply may be caused by a marked increase in caloric consumption of alcohol or sugar. Presumably the same relationship might exist with fat.

Numerous observations now exist in the United States to indicate that acute fatty cirrhosis will undergo excellent histologic repair coincident with clinical improvement when the patient is simply fed a basal hospital diet without vitamin or lipotropic supplements, rested, and removed from alcohol [Buck (92), Volwiler, Jones & Mallory (93); Klatskin & Yesner (94)]. Presumably the basal diet ingested during these observations contained a supply of lipotropic agents and sulfur-containing amino acids adequate for hepatic cell repair. Some of Klatskin's patients received only 55 gm. of mixed protein daily. *Evidence has accumulated to indicate that the daily fat intake of the patient with fatty cirrhosis or infectious hepatitis need not be restricted if the remainder of the diet be adequate in protein and lipotropic agents* [Volwiler *et al.* (93); Hoagland *et al.* (95)]. The reviewer has recently observed two adult males with acute fatty cirrhosis making good histologic repairs including loss of fat vacuolization of hepatic cells while receiving a daily diet of 55 gm of protein and 270 gm. of fat.

The addition of lipotropic agents [Kinsell *et al.* (96)] or of testosterone [Rosenak, Moser & Kilgore (97) and Kinsell (98)] has been reported to cause extra and supposedly beneficial nitrogen retention in ill, cirrhotic patients. Other similar experiments by Gabuzda and associates (99), however, suggest that the nitrogen retention resulting from lipotropic supplementation is negligible and the nitrogen retention resulting from the use of testosterone is less than can be easily obtained by a moderate increase in protein intake alone

Fluid Retention in Cirrhosis

The abnormal fluid retention of most cirrhotic patients having ascites and edema may be controlled by dietary sodium restriction [Eisenmenger *et al.* (100, 101), Gabuzda *et al* (102), Layne & Schemm (103), Faloon *et al* (104), Goodyer *et al* (105), Nelson *et al* (106), Holley & McLester (107), Kark (108), and Lowe & Overy (109)] The intake of sodium has been shown to determine the rate of accumulation of the ascites [Eisenmenger and coauthors (100)] Urinary, sweat, and salivary excretion of sodium during periods of edema fluid reaccumulation fall to a very low figure [Eisenmenger *et al.* (100) and Gabuzda *et al* (102)], reflecting strenuous effort throughout the body to retain sodium. Rapid reaccumulation of ascitic fluid after paracentesis may result in withdrawal of sufficient plasma sodium to produce hyponatremia [Eisenmenger *et al.* (100) and Gabuzda *et al.* (102)] This can occasionally occur to a degree sufficient to produce clinical symptoms [Nelson

hyperglycemia with or without secondary symptomatic hypoglycemic rebound. Stasis with distention may sometimes occur in the afferent jejunal loop or in the gastric remnant, causing regurgitation of food and bile as well as pain, fullness, and nausea. Permanent elevation of intragastric pH is alleged to encourage bacterial growth and promote destruction of members of the B group of vitamins [Welbourn *et al.* (81)]. Megaloblastic anemia has occasionally followed wide gastric resection and responded to vitamin B_{12} and folic acid therapy [Conway & Conway (82)] Whereas voluntary limitation of food intake is largely responsible for most of the clinical features of malnutrition following gastric resection, malabsorption of fat in some individuals causes a very significant loss of calories [Wollaeger (83); Wollaeger *et al.* (84); Jones *et al.* (85)]. Recent data on such steatorrhea is presented by Brain & Stammers (79), who consider the principal cause of this fat loss to be inadequate mixing of food with bile and pancreatic juice. In support of this concept are the observations of Wollaeger (83) indicating that patients with Billroth I anastomoses (gastroduodenostomy) do not have as much steatorrhea as those with Billroth II anastomoses (gastrojejunostomy). It is reported [Brain & Stammers (79)] that doubling the fat intake of these patients often doubles the amount of fat absorbed, the percentage of loss remaining approximately constant, in some cases dividing daily fat intake into multiple small portions was reported to increase the percentage absorbed. Successful attempts to replace the lost reservoir function of the resected stomach by substituting portions of the colon, anastomosed between esophagus or gastric remnant and duodenum, have been reported by Moroney (86) and by Lee (87).

LIVER DISEASE

Nutritional Liver Disease

An excellent review of knowledge relating nutrition and disease of the liver is provided by Davidson & Gabuzda (88) Striking relation between nutritional deficiency and Laennec's cirrhosis exists in many parts of the world, examples being reported from India, Jamaica, Peru, and South Africa. In these geographic areas, alcoholism is not a factor in the production of the disease In these human nutritional deficiencies, the exact mechanisms responsible for the pathogenesis of the liver disease are not well understood. Presumably those dietary factors are implicated which, when omitted, have been well demonstrated to cause nutritional liver disease in laboratory animals This broad group of specific compounds now includes methionine, cystine, choline, vitamin E, and vitamin B_{12} The large body of experimental work leading to recognition of the relationship of these substances to liver cell injury has recently been reviewed by György (89) and by Best (90). Vitamin B_{12} may be the beneficial ingredient of the various liver extracts claimed by various clinical investigators to have therapeutic benefit in fatty cirrhosis [Gyorgy (89)]

Davidson & Gabuzda (88) conclude that simple starvation probably does

should exist, the best undoubtedly being the demonstration of esophageal varices.

Further reports of follow-up studies in patients undergoing porta-caval shunt operations have been published by Blakemore (120, 121, 122), Linton (123, 124), MacPherson (125), Gammeltoft (126), and Gerbode & Holman (127). The mortality of this procedure is progressively lower as experience in the operation is achieved and a better understanding of the proper selection of the patient is gained. At present, it appears that the operative mortality in patients with extrahepatic portal bed block is less than 4 per cent and for cirrhotics with reasonable hepatic function (no active liver disease, serum albumin greater than 3.0 gm. per cent, normal plasma prothrombin concentration) is less than 18 per cent. The results of the procedure are encouraging to date, and it seems thus far the most logical surgical attack on the problem of portal hypertension. It is unfortunate that no adequate mortality figures in patients with untreated esophageal varices have ever been printed, and that no satisfactory figures clearly separating the results of splenectomy alone in each of the two types of portal hypertension (intrahepatic and extrahepatic in origin) have been published with which to compare the results of present-day porta-caval shunt procedures. Linton (124) discusses in detail the correlation between liver function tests and operative mortality in his cases of cirrhosis. Linton's rather dismal feelings regarding the operative hazard in cirrhotics with ascites are not shared by Blakemore (122); the reviewer would agree heartily with Linton that operation should not be done primarily for ascites unless this had been shown to fail to respond to excellent medical management. Blakemore (122) reports that ascites was regularly relieved in his patients following porta-caval shunt

Although splenectomy alone will cure those few patients having congestive splenomegaly due to splenic vein thrombosis, by destroying the neighboring length of splenic vein, it commonly prevents the later accomplishment of an adequate spleno-renal vein anastomosis; the latter appears to be the present procedure of choice if thrombosis of the portal vein itself exists. In Blakemore's recent series of 40 cases of portal hypertension due to extrahepatic portal block, the site of obstruction in each instance was in the portal vein itself; in only one instance was Blakemore able to use the portal vein for the anastomosis [Blakemore & Fitzpatrick (121)]. In this publication, the authors review their problems in dealing with the postsplenectomy bleeder who has extrahepatic portal hypertension They present as a possible solution the technique of femoral vein graft between splenic vein stump and left renal vein. A means of postoperative regional heparinization of the vein-grafted area is also given

Crile (128) and Linton (124) have both reported satisfactory experience in direct transesophageal ligation of bleeding esophageal varices. Linton has used this procedure to allow improvement in the general condition of the patient prior to porta-caval shunting. Esophageal varices do not necessarily disappear following successful porta-caval shunt [Linton (124)]. Fatal hemor-

et al. (106), Holley & McLester (107), Kark (108), and Lowe & Overy (109)]. Low serum sodium concentrations are not uncommonly found in cirrhosis with marked ascites These may not return to normal until edema and ascites disappear. [Eisenmenger *et al.* (100)].

Cation exchange resins offer hope as useful tools for sodium withdrawal from the body in managing edema accumulations in chronic liver disease as well as in congestive failure and nephrosis. Two useful reviews of this subject have appeared [Dock & Frank (110) and McChesney *et al.* (111)]. To date, such resin treatment is not uniformly effective. It must be used in conjunction with dietary sodium restriction and may sometimes produce profound electrolyte disturbances, particularly hypopotassemia. The daily amounts required for effectiveness are large and may cause mild gastrointestinal disturbances.

Chalmers, Eckhardt & Davidson (112) review experience in 17 patients whose ascites was treated by insertion into the abdominal wall of a peritoneal button with intent to drain ascitic fluid subcutaneously. Five cases were benefited for varying lengths of time. In the 10 autopsied patients, all buttons were carefully examined and considered to be nonfunctional.

Portal Hypertension

An excellent comprehensive review of recent work in all phases of this subject has been published by Welch (113). The anatomy of the extrahepatic portal vein and its tributaries is reviewed and new original material on the subject presented by Douglass, Baggenstoss & Hollinshead (114), by Gilfillan (115), and by Edwards (116). The work of Douglass presents measurements of configurations encountered in careful dissection of 92 human cadaver specimens, together with many practical anatomic conclusions which should be of considerable interest to surgeons who operate in this area. Gilfillan reports similar data on 59 dissections. The work of Edwards (116) particularly emphasizes the importance of the deep-lying, porta-systemic communications in the development of collaterals to an obstructed portal vein.

A new concept of the mechanism for development of portal hypertension in cirrhosis of the liver is given by experimental observations of Kelty, Baggenstoss & Butt (117). Rather than simple compression of intrahepatic portal radicles by scar tissue alone, the expanding nodules of regeneration themselves may also obstruct major portal tributaries.

Cumulative experimental and clinical data concerning the relationship between portal vein pressure and ascites formation are reviewed by Volwiler, Grindlay & Bollman (118) and by Volwiler (119) There appears to be no necessary direct relationship between portal pressure and the development of ascites. Lymphatic engorgement, increased capillary permeability, or low tissue tension may likewise be important local mechanical factors influencing the localization of edema fluid in the peritoneal cavity Thus surgery to lower portal pressure is not indicated by the mere presence of ascites; other, more reliable criteria of the presence of portal hypertension in a given patient

responsible for this chemical transformation. Aureomycin in usual therapeutic doses, by markedly inhibiting bacterial growth, causes the virtual disappearance of urobilinogen from urine and feces [Sborov, Jay & Watson (136)] Clinicians not recognizing these facts may readily be confused by laboratory urobilinogen reports in jaundiced patients receiving this or a similar antibiotic.

Serum cholinesterase and albumin—The development of the simple potentiometric method of Michel (137) has furthered clinical exploration of determinations of serum esterase activity in hepatobiliary diseases. Its usefulness in following serially the progress of patients with chronic advanced liver disease or acute hepatitis is now well established. The best recent reports on this subject have been made by Vorhaus and co-workers (138, 139).

The marked correlation between the serum albumin concentration and serum esterase activity was first described well by Faber (140). The parallelism of the two protein levels in patients with infectious hepatitis and cirrhosis was pointed out by Kunkel & Ward (141). Recent work by Levine & Hoyt (142) and by Fremont-Smith & Volwiler (143) indicates that this correlation holds in almost any pathologic condition except in patients with marked albuminuria. During the progress of chronic hepatic disease changes either in the value for albumin or for esterase are quickly paralleled by appropriate alteration of the other. Presumably the two circulating protein molecules are made by closely allied processes within the hepatic cell. It is the conclusion of many workers in this field that serial determination of either serum albumin or esterase may well be the most useful laboratory observation to be made in following the progress of the patient with chronic advanced liver disease.

Bromsulfalein[3] test in gastrointestinal hemorrhage.—There is constantly a need for differentiating those patients with severe liver disease who may have bleeding esophageal varices from individuals bleeding from other sources. Zamcheck *et al* (144) report favorably upon their experiences with the Bromsulfalein test performed during or very soon after severe bleeding. Continued high retention was observed in patients with proven advanced cirrhosis, but in no other disease Slight retention, falling to normal after disappearance of shock, was not uncommon in patients with mild liver disease or without known liver disease. In the reviewer's experience, the results are generally quite as reported, occasionally one discovers a compensated cirrhotic with normal Bromsulfalein retention who has developed portal hypertension, esophageal varices, and hemorrhage, but such instances are not common.

PANCREATIC DISEASE

Tests of pancreatic function—Review articles dealing with various features of this subject have appeared [Cattell & Warren (145), Wirts & Snape

[3] Bromsulfalein (sulfobromophthalein U.S.P.).

rhage from a varix in the presence of a very large, spontaneously formed porta-caval anastomosis is reported by Beswick & Butler (129). One therefore wonders if a later direct attack upon the varices as described by Crile will be found necessary in many postoperative shunt cases

A novel, new surgical attack on the problem of portal hypertension is the simple ligation of both hepatic and splenic arteries; successful accomplishment of this in six cases of cirrhosis is reported by Rienhoff (130). The premise for this approach rests in the concepts (*a*) that hepatic arterial flow into the liver contributes materially to the elevation of the portal vein pressure, and that (*b*) splenic blood flow contributes importantly to portal vein load Clinical and experimental experience in ligation of the hepatic artery and its branches is presented and reviewed by Markowitz (131) and Markowitz & Rappaport (132) The practice of simple ligation of the splenic artery alone in the hope of materially lessening the portal vein inflow has in recent years been revived for certain cases. The defeat of this approach by enlargement of numerous already existing arterial collaterals is pointed out by Learmonth (133).

Primary Biliary Cirrhosis

This disease syndrome (previously termed Hanot's hypertrophic biliary cirrhosis, xanthomatous biliary cirrhosis, pericholangitic biliary cirrhosis) has been further rescued from its former state of confusion with related biliary tract diseases by the important monograph of Ahrens, Payne, Kunkel, Eisenmenger & Blondheim (134) Their work appears to represent the clearest review and most complete study thus far reported on this subject.

According to this group of investigators, primary biliary cirrhosis appears to be a specific distinctive disease occurring chiefly in adult females, not associated with disorders of the extrahepatic biliary tree, and is of unknown cause. It is characterized by long-standing itching and jaundice, by marked hepatomegaly, variable degrees of splenomegaly, and a relentless prolonged course. Liver function remains good until late in the disease All patients exhibit elevation of serum lipids of varying degree However, only a small proportion develop generalized xanthomatosis, this feature of the disease syndrome appears when serum total lipid exceeds 1,800 mg per cent Well-developed xanthomata resolve spontaneously when the serum lipid level later falls. Death eventually results from hepatic failure or massive hemorrhage from esophageal varices All patients have steatorrhea and most develop osteoporosis. To be differentiated from this disorder is biliary cirrhosis developing as a result of extrahepatic biliary duct disease. Elevation of the total serum lipid concentration occurs in the course of this disease too and may here also reach levels sufficiently high to result in generalized xanthomatosis.

Liver Function Tests

Urobilinogen.—Hollan (135) has found that the colon is the site of formation of urobilinogen from bilirubin in the normal adult. Bacterial action is

second and third days postoperative electric stimulation was applied. Pain arising from the head of the pancreas was right-sided and distributed from the sixth to the eleventh thoracic dermatome. That from the body of the organ was of bilateral nerve distribution and tended to be midline. Pain from stimulation of the tail area was referred to the left of the midline and was largely abolished by left splanchnic block. Simultaneous stimulation in all three areas resulted in severe band-like pain radiating through to the back. The findings of this excellent investigation supplement very well previous observations on pancreatic afferent pain pathways reported by Ray *et al.* (157, 158).

Pancreatitis.—Further support to the biliary regurgitation concept of origin of pancreatitis is given by recent work of Howell & Bergh (159). In 25 of 27 patients showing diodrast regurgitation into pancreatic ducts during cholangiography, an elevation of serum amylase occurred. Wainwright (160) developed an alternative explanation of origin of pancreatitis based on intrapancreatic duct obstruction as the major factor. This concept holds that a rise in secretory pressure behind a partial ductal obstruction may cause rupture of small numbers of acini, liberating active enzymes sufficient to start a chain enzyme reaction; this may then spread to involve wide areas of the pancreas. Gage & Gillespie (161) developed the theory of spasm of the sphincter of Oddi as important to the production or continuation of acute pancreatic necrosis. These authors advocate bilateral splanchnic block in the hope of relaxing the sphincter as well as blocking afferent visceral pain fibers. Experimental and clinical data are offered to support their conclusion that this procedure may also arrest the progression of the acute attack and thereby lower mortality rate. The idea is attractive but will require further investigation for sound acceptance.

THE STEATORRHEAS

Increasing interest and attention has been given in recent years to the broad group of gastrointestinal disorders producing abnormal loss of fat in the feces The major clinical manifestations of defective fat absorption, aside from diarrhea, are loss of weight and development of fat-soluble vitamin deficiencies, notably vitamins D and K.

Recent publications of Albright & Stewart (162), of Frazer (163), and of Ingelfinger (164) deal particularly with the problem of avitaminosis in steatorrhea syndromes. Frazer (163) puts forth the theory of bacterial competition with the host for essential metabolites as an explanation for the deficiency of vitamins, alternative to the classic theory of primary malabsorption. Frazer (165) has repeatedly pointed out the unusually high ascent into the small intestine of bacterial growth in the presence of steatorrhea.

Gross steatorrhea is easily recognized by simple inspection and laboratory study of a single stool specimen. Less severe degrees of fat loss, grossly undetectable but nevertheless causing important loss of dietary calories, may

(146), and Nothman (147)]. Bethanechol (urecholine; urethane of β-methylcholine chloride) has been shown to stimulate the human pancreas to produce secretion rich in enzymes and of increased viscosity, similar to that previously obtained with methacholine bromide (Mecholyl) [Kyle *et al.* (148)] Experience in analyzing duodenal contents following injection of secretin in a large group of patients having tumors of the pancreas is reported [Dreiling (149)]. The most consistent abnormality found was a diminution from the normal response in secretory volume. Tumors encroaching on main ducts produced abnormal findings. There was considerable variability in data, normal values being found several times in the presence of extensive neoplasm.

Determinations of serum amylase and lipase after secretin injection in patients with pancreatic disease are presented by Lopusniak & Bockus (150). Rises occur in individuals having active acinar tissue distal to pathology of an obstructive type, inflammatory or neoplastic. The authors suggest use of the test in selected individuals with obscure abdominal pain suspected of pancreatic pathology. Administration of opiates, even codeine, to the normal individual may result in a rise in titer of serum amylase and lipase [Gross *et al.* (151)]. This is of particular interest with reference to recent reports of administration of secretin plus opiate to detect pancreatic disease through a rising titer of blood enzymes [Wirts & Snape (146)]: Where functioning acinar tissue lies distal to obstructive pathology, the rise in titer is much higher than in the normal. Complete destruction of the pancreas causes low basal values without subsequent rise.

The parallelism between serum and urine amylase levels during the course of acute pancreatitis is again described [Dankner & Heifetz (152)]. Decrease in glomerular filtration during dehydration and shock is logically held responsible for occasional situations in which urine titers remain normal while serum values are rapidly rising; a delayed rise of urine values occurs after rehydration. Bowen (153) shows that amylase assay of aspirated intraperitoneal fluid may confirm the suspicion of acute pancreatitis.

A seemingly important modification of the gelatin film test for stool tryptic activity is described [Johnstone & Neter (154)]. This test has achieved rather widespread popularity in pediatric clinics as a rough screening method for detecting cases of cystic fibrosis of the pancreas Frequent instances are presented of false positive results due to the presence in stools of gelatin-liquefying bacteria. False negatives are not so common in infants as in adults, but even in pediatric practice tryptic activity may occasionally be lacking in the stool although present in duodenal juice. Diminished bowel motility with enzymatic destruction of trypsin during transit is suggested as the explanation [Schwachman (155)].

Pancreatic pain.—The localization of pain referred from various areas of the pancreas was studied by Bliss *et al.* (156) through an ingenious technique: At laparotomy, electrodes were introduced into the head, body, and tail of the gland and brought to the outside through a stab wound On the

practice of placing all patients having steatorrhea on low fat diets. Their data show fat absorption, though impaired, to remain proportionate to fat intake even at high levels Nutritional advantages to an increased daily fat absorption are pointed out, and the authors seldom noted deleterious effects from normal fat intake levels.

An explanation for the usual "deficiency pattern" in small bowel barium x-rays of steatorrhea patients is given by Ardran and co-workers (176): the "deficiency pattern" is the result of the flocculation of usual barium sulfate suspensions by excessive intraluminal mucus. The excessive production of mucoid secretions by the small intestine as a result of mucosal stimulation from increased free fatty acids has been pointed out by Frazer (165). In sprue patients, Ardran *et al* find either normal or abnormal mucosal patterns at will, depending upon the type of barium sulfate suspension employed in the radiologic examination

AMEBIASIS

Increasing recognition is being given to the prevalence of this disease in all parts of the United States. Ability to recognize and confirm the diagnosis depends upon adequate stool examinations by technicians sufficiently experienced and well-trained in specific techniques to be reliable; such individuals are uncommon in the usual large practicing hospitals. Comparative experiences of a trained team with several laboratory techniques widely used in the search for the ameba are reported by Young *et al.* (177). Even when adequate examinations are carried out, many cases of active infestation remain unconfirmed; thus, the policy should be continued of giving selected patients a therapeutic trial of amebacidal agents if serious suspicion of the existence of amebiasis exists Continuance of the intestinal infestation after one or, indeed, several courses of therapeutic agents used singly or in combination occurs in at least 10 to 15 per cent of cases.

An excellent basic review of the pharmacologic basis of chemotherapy for amebiasis is presented by Anderson & Hansen (178) A very complete clinical review of the treatment of amebiasis is given by Bargen (179). Further laboratory and clinical experience with aureomycin, terramycin, bacitracin and chloramphenicol in the treatment of intestinal amebiasis is reported by Most and co-workers (180, 181, 182), by Hoekenga (183), by Hall (184), by Conn (185), and by Conan (186) These antibiotics probably have some direct amebacidal action, although their major role is to suppress bacterial growth, upon which the ameba depends for nutrients Since most patients with intestinal amebiasis may be expected to have some secondary bacterial invasion of the amebic lesions, the use of one of these antibiotics in any well-planned therapeutic program for acute amebiasis seems indicated In the studies in which the antibiotic has been used alone, terramycin in adult dosage of 2 0 gm. daily for 10 days, has been found more effective than the remainder of the group Aureomycin appears nearly as satisfactory, whereas bacitracin and chloramphenicol are reported to be only moderately effica-

require carefully conducted balance studies for their demonstration. Even in the normal individual, fat absorption on a standard regimen is often found to vary as much as 30 per cent during successive four-day collection periods [Fourman *et al.* (166)]. Variations in individuals with clinical sprue may be wider, making very difficult accurate appraisal of therapeutic programs. Undoubtedly many instances of transient symptomatic mild steatorrhea pass unrecognized.

Because of the complexities of the digestion and absorption of fat in the gastrointestinal tract, involving both emulsification and lipolysis, it would be expected that steatorrhea would result from disease in any one of several organs of the gastrointestinal system. Specific general causes are (*a*) lack of production of bile salts for proper emulsification of fats, (*b*) lack of production of pancreatic lipolytic enzymes, (*c*) short-circuiting of the food stream so as to produce inadequate mixing with bile and pancreatic juice, (*d*) impaired absorptive function of the small intestine. It has long been well recognized that complete obstructive jaundice results in excessive fat loss through absence of bile salts in the high intestine Gross and co-workers (167) report balance data to show that transient steatorrhea occurs in acute hepatitis, presumably from temporary lack of production of bile salts by the damaged liver. Pancreatic function studies in these cases were normal [Gross *et al.* (168)] Whereas in these patients the steatorrhea found was not of sufficient magnitude to be clinically important, in the primary biliary cirrhosis studies reported by Ahrens *et al.* (134), osteomalacia and cachexia were presumably caused in part by the excessive loss of fat in the feces

Metabolic balance studies in an individual having but 2½ ft of normal small bowel are reported by Christensen *et al* (169). Fat absorbing ability was decreased by only 20 per cent from the normal when tested on a standard 101 gm fat intake daily, this is less of a steatorrhea than found in most sprue during exacerbation. Althausen *et al.* (170) report in two patients undergoing massive small bowel resection striking physiologic readjustments with slow but progressively increasing ability to absorb nutritional materials.

Fourman *et al.* (166) point out that determining the ratio of neutral fat to free fatty acids in feces to differentiate between pancreatic insufficiency and sprue is quite useless; in patients with advanced pancreatic disease sufficient lipolytic activity from intestinal secretions or bacterial products is generally present to cause splitting of most neutral fat prior to laboratory determination.

Whereas folic acid has produced striking symptomatic remission with subsidence of steatorrhea in some instances of idiopathic steatorrhea (sprue) [Darby *et al.* (171); Spies *et al* (172); Fourman *et al.* (166)], complete failures have commonly been the experience of others [Jones & Ellis (173), Weir & Comfort (174)]. Difficulties in interpreting response of sprue patients to various hospital regimens are pointed out by Christensen *et al.* (169); spontaneous remission often ensues from simple hospitalization and forced feeding of a generally good diet. Chung *et al.* (175) seriously question the standard

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cious. The results obtained with terramycin and aureomycin are quite comparable to the best data ever reported from using the older drugs such as carbarsone or emetine bismuth iodide. Equally satisfactory results in intestinal amebiasis from the use of bismuth glycolylarsanilate (Milibis) are reported by Conn (185, 187) and Berberian *et al.* (188).

Further reports of the dramatic efficacy of chloroquine in hepatic amebiasis are provided by Sodeman *et al.* (189). A warning against using aureomycin alone when the possibility of hepatic amebiasis co-exists is given by Hall (184); the hepatic lesions were found relatively unaffected by this antibiotic.

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DISEASES OF THE CARDIOVASCULAR SYSTEM[1]

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Methods of Diagnosis

Phonocardiography, a diagnostic procedure introduced by Einthoven in 1894, was employed by Counihan *et al.* (1) to determine the cause of the initial vibrations of the first heart sound. These low frequency, low amplitude vibrations are commonly thought to be due to atrial systole. The authors observed that these initial vibrations appeared, however, even though the atria were fibrillating and even though atrial and ventricular systole were widely separated because of heart block. These data suggested that the initial vibrations might be caused by the onset of ventricular contraction through mechanisms unrelated to atrial contraction, the movement of the heart in the chest, or the taking up of slack in the chordae tendineae and atrioventricular valves before closure Phonocardiography was also employed by Ravin & Darley (2) for the study of apical diastolic murmurs which occurred in certain patients with patent ductus arteriosus. The murmurs were similar to the mid-diastolic rumble of mitral stenosis, being low-pitched, located at the cardiac apex, and best heard with the patient in the left lateral decubitus position after exercise. The presence of these murmurs was explained by: (*a*) enlargement of the left ventricle causing a relative narrowing of the mitral orifice, (*b*) a large volume of blood traversing the mitral valve at a high rate of flow, or (*c*) a thin chest wall which makes blood turbulence more audible.

Cardiac catheterization has been widely employed during the past year, particularly in the field of acquired heart disease, and techniques have been improved with the development of recording instruments of high fidelity Ellis, Gauer & Wood (3) supplied a method for recording pressure tracings by means of a miniature intracardiac manometer. Excellent illustrations of artifact-free pulse waves from within the heart and great vessels of humans and dogs were illustrated. Helmsworth *et al.* (4) visualized the coronary arteries during life by retrograde catheterization of the carotid and brachial arteries in five patients Small polyethylene or woven catheters were inserted into the ascending aorta, Diodrast (iodopyracet) or Neo-Iopax (sodium iodomethamate) was forcibly injected and serial roentgenograms were taken The large and small branches of the coronary arteries were demonstrated among normal subjects, and failure of the coronary vessels to fill after ligation was demonstrated in 10 dogs.

[1] This review covers many, but not all, of the contributions published in a period from September, 1950, to September, 1951. The abbreviation *et al* is used when more than three authors' names appear on a paper

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serious impairment of ventricular function, such as might occur with myocardial infarction, cardiac failure, pericarditis, or myocarditis; and (*c*) abnormalities of individual strokes occurred in certain specific situations including hypotension (shallow K waves), hypertension without heart disease (deep K waves), angina pectoris (increased variations in amplitudes with respiration), coarctation of the aorta (deep I and shallow K waves), and in hypertension with heart disease (low amplitude in expiration with shallow I-J and deep K waves). The respiratory variation index (inspiratory minute volume minus expiratory minute volume divided by surface area) was of value in patients with coronary insufficiency who did not have elevated arterial pressures and who had not had a coronary occlusion. The index was higher than 450 in all patients with coronary insufficiency. The authors described four grades of abnormality, namely, Grades I, II, III, and IV, the latter being the most severe (*vide infra*). Mathers *et al.* (16), employing a low frequency, critically damped, table type ballistocardiograph [Nickerson & Curtis (17)] which had been calibrated for cardiac output against the method employing the Fick principle, showed that most patients with myocardial disease demonstrated a definite deviation of the ballistocardiographic pattern from the normal which reflected the mechanical dysfunction of the heart and not a specific etiology. Changes in the degree of myocardial insufficiency produced parallel changes in the ballistocardiogram. Records obtained with this instrument provided an objective method of evaluating therapy designed to improve the mechanical efficiency of the myocardium.

Dock, Mandelbaum & Mandelbaum (18) described a portable electromagnetic ballistocardiograph which recorded the relative movement between a coil and a magnet. Their clinical studies on aortic insufficiency showed high I-J waves which were unaccompanied by a corresponding increase in stroke volume, indicating that the ballistocardiogram is not an accurate measure of cardiac output in this condition. They found a high incidence of angina pectoris, myocardial infarction, and myocardial scars among patients with tracings showing pronounced respiratory variations or complete obliteration of the normal pattern. Ballistocardiograms of patients with congestive heart failure showed either high or low amplitude of the I-J waves. The former was usually due to beriberi, toxic diffuse goiter, arteriovenous fistula, or anemia, while the latter was due to myocardial infarction, myocarditis, or advanced coronary insufficiency Anemia with heart failure was associated with waves that were large but which became low and bizarre as hemoglobin levels returned to normal Acute myocarditis was frequently accompanied by decided ballistocardiographic abnormalities which were the only objective evidence of cardiac involvement. The routine ballistocardiogram was recorded under basal conditions with the patient: (*a*) breathing normally, (*b*) holding his breath in deep inspiration, and (*c*) holding his breath in deep expiration. In suspected cardiac cases in which these records were normal, the sequence was repeated after exercise. The tracings were diagnosed as normal or as showing a definite abnormality, a marked abnor-

Electroretinography was advocated by Henkes (5) as a method for determining the circulatory status of the retina. The author stated that the shape of the electroretinogram was largely dependent upon changes in retinal circulation as shown by the altered curve which followed the intravenous injection of 1 cc. of Priscoline (2-benzyl-imidazoline hydrochloride; benzazoline).

Radioactive sodium clearance rates following intramuscular injection was considered by Semple, McDonald & Ekins (6) to be an inaccurate measure of local blood flow because of the poor correlation with claudication time. On the other hand, Wisham, Yalow & Freund (7) showed that the clearance rate of radioactive sodium from the gastrocnemius muscle was reproducible over periods of time up to three months Exercise increased and posture had no effect on the rate of clearance.

Angiocardiography by direct puncture was employed by Nunez & Ponsdomenech (8) 45 times in 30 patients without mortality or ill effects. The value of angiocardiography carried out in the conventional manner in the differentiation of ventricular aneurysm, pericardial cyst, or extra-cardiac neoplasm invading the heart was pointed out by Kammerling, Cavenagh & Unger (9). Prominence of the pulmonary artery segment in the angiocardiogram was studied by Miller (10). This was due to: (*a*) idiopathic dilatation of the pulmonary artery, (*b*) pulmonary artery aneurysm, (*c*) patent ductus arteriosus, (*d*) interatrial septal defect, or (*e*) Eisenmenger's complex.

Blood volume analysis using the dye T1824 was simplified by Shapiro (11). Nelson *et al.* (12), using this method, demonstrated that optimal body weight forms an accurate basis for determining the standard physiologic vascular capacity. They administered preoperative volumetric replacement of volume deficits by daily transfusions of whole blood. Operative and postoperative blood losses were replaced by transfusion during and following surgery. Price (13) pointed out that the most satisfactory way of determining the total blood volume was to measure the plasma volume and the cell volume separately and to take the sum of the two. Low blood volume occurred in acute blood loss, cachexia, eclampsia, toxic goiter, nephritis, artificial fever, heatstroke, septicemia, certain biological and chemical poisonings, and other conditions. Low plasma volume was found in dehydration and in those conditions characterized by escape of plasma or serum from the vascular bed (for example, burns, peritonitis, or venous obstruction). A normal plasma volume was found in chronic blood loss.

Ballistocardiography, a method for graphically recording the motion of the body with each heart beat, was originally described by Gordon (14) 74 years ago During the past year the empiric correlation of the ballistocardiogram with various clinical states has been studied enthusiastically by several authors. Brown & de Lalla (15), using a high frequency, table type

serious impairment of ventricular function, such as might occur with myocardial infarction, cardiac failure, pericarditis, or myocarditis; and (*c*) abnormalities of individual strokes occurred in certain specific situations including hypotension (shallow K waves), hypertension without heart disease (deep K waves), angina pectoris (increased variations in amplitudes with respiration), coarctation of the aorta (deep I and shallow K waves), and in hypertension with heart disease (low amplitude in expiration with shallow I-J and deep K waves). The respiratory variation index (inspiratory minute volume minus expiratory minute volume divided by surface area) was of value in patients with coronary insufficiency who did not have elevated arterial pressures and who had not had a coronary occlusion. The index was higher than 450 in all patients with coronary insufficiency. The authors described four grades of abnormality, namely, Grades I, II, III, and IV, the latter being the most severe (*vide infra*). Mathers *et al.* (16), employing a low frequency, critically damped, table type ballistocardiograph [Nickerson & Curtis (17)] which had been calibrated for cardiac output against the method employing the Fick principle, showed that most patients with myocardial disease demonstrated a definite deviation of the ballistocardiographic pattern from the normal which reflected the mechanical dysfunction of the heart and not a specific etiology. Changes in the degree of myocardial insufficiency produced parallel changes in the ballistocardiogram Records obtained with this instrument provided an objective method of evaluating therapy designed to improve the mechanical efficiency of the myocardium.

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mality, or a maximum abnormality. Tracings which showed definite abnormalities were those which at rest or after exercise showed unusual respiratory variations with good amplitude during inspiration [Brown (15), Grades I and II]. Tracings which showed marked abnormalities were those which at rest or after exercise showed notched J waves or low amplitude, irregular I-J waves which became unidentifiable in expiration [Brown (15), Grade III]. Tracings which showed maximum abnormalities included those with totally abnormal complexes of low amplitude under basal conditions (Brown (15), Grade IV). Mandelbaum & Mandelbaum (19), using the Dock ballistocardiograph, found this technique helpful in evaluating the recovery of the myocardium after coronary thrombosis. De Lalla, Epstein & Brown (20) studied the H waves of the ballistocardiograms of patients with complete heart block and atrial fibrillation. As H waves were seen without normal atrial contraction, it seemed probable that they represented a force produced at least in part by the apex thrust of the heart. Braunstein, Oekler & Gowdy (21) described a ballistocardiograph with two degrees of freedom corresponding to the frontal plane of the body.

Plethysmography was employed by Winsor (22), using the Burch pneumoplethysmograph, to describe the vasomotor reactions of the toe tip following arterial occlusion at the ankle for 15 min. In normal subjects, following release of arterial occlusion the relative rate of blood flow of the toe rose to a high level which was well above that of the resting flow, reaching its peak within 1 min. Among patients with arteriosclerosis obliterans, the relative rate of blood flow rose to a low level, slightly above that of the resting flow, reaching its peak in 3 or 4 min. This technique was suitable for measuring the arterial reserve in patients with peripheral vascular disease and as a means of selecting patients for lumbar sympathectomy since it could be carried out satisfactorily by a well-trained technician. Blood flow studies also were carried out by Mendlowitz (23), who employed the calorimetric method for measuring the blood flow of the finger tip. He determined the vascular resistance of the finger tip of patients with polycythemia and hypertension. In polycythemia, the resistance was often increased before, and decreased after, phlebotomy. In well-established hypertension, resistance was increased The relationship between pressure in the brachial artery and blood flow in the finger tip was found to be rectilinear.

Electrokymography, originally described by Henny & Boone (24) in 1945, has found much clinical application in the past year. Schwedel, Samet & Mednick (25) stated that the electrokymogram was of aid in supporting the diagnosis of myocardial infarction in the presence of left bundle branch block where paradoxical pulsations of the left ventricle were present. Such pulsations may be present, however, in enlarged hearts without infarction. Phillips (26) stated that paradoxical pulsations or failure of pulsations of the left ventricle have also been encountered in patients with myasthenia gravis, progressive muscular dystrophy, angina pectoris, and certain subjects without heart disease In patients with aortic insufficiency there was shortening or abolition of the isometric relaxation phase (the period preceding ventricu-

lar filling during which time the ventricle is a closed chamber and no volumetric changes are occurring). Ventricular hypertrophy without signs of congestive heart failure was associated with prolongation of the isometric relaxation phase which was one of the early signs of muscular fatigue. This phase was shortened by digitalis. Studies of the pulsations of the left atrium in normal and diseased hearts were made by McKinnon & Friedman (27). A characteristic abnormality of the electrokymogram observed in patients with organic mitral valvular insufficiency gave graphic evidence of regurgitation of blood from ventricle into atrium. Electrokymographic evidence of mitral regurgitation was found in certain persons with mitral stenosis who did not have an audible systolic murmur. Patients with Austin-Flint murmurs, and individuals with murmurs mimicking mitral insufficiency, showed normal atrial pulsations.

The Wolff-Parkinson-White syndrome was studied by Samet, Mednick & Schwedel (28) by recording simultaneously the electrocardiogram and the electrokymograms from the ascending aorta and pulmonary artery. Mechanical asynchronism was found in only 5 of 15 cases, but delay in ejection from both ventricles, regardless of the site of the bundle of Kent, was found in most instances. Dack, Paley & Brahms (29) also recognized a lack of significant asynchronism in right and left ventricular contraction in patients with Wolff-Parkinson-White syndrome. It was theorized that asynchronism did not occur because the early aberrant impulse traveled more slowly through the ventricular muscle than the normal impulse traveled through the His-Purkinje system. Thus, the premature excitation of the affected ventricle was offset by the slower propagation of the aberrant excitation wave. Willis *et al.* (30) pointed out the importance of measurements of duration rather than amplitude and configuration in electrokymographic studies. Special attention was directed to the increased duration of the isometric relaxation phase which occurred in the presence of cardiac disease.

Vectorcardiography, originated by Mann (31) in 1920, has stimulated widespread interest and intensive study during the past year. Grant & Estes (32), in a small book entitled *Spatial Vector Electrocardiography*, described a method for determining a spatial vector in which the various limb and precordial leads were treated as different perspectives or points of vantage in visualizing a three-dimensional electric field. They derived the spatial QRS vectorcardiogram from the standard leads and the precordial lead which showed equiphasic QRS complexes. The procedure was as follows: the frontal [illegible]

cordial lead and the center of which passed through the center of the heart at the origin of ÂQRS; the vector and the plane were then adjusted, keeping the positions already determined intact, until they were perpendicular to each other. Thus the vector assumed a spatial position and the plane divided the body into its approximate electric fields.

Graybiel (33) reported a method for determining the directions of the

mality, or a maximum abnormality. Tracings which showed definite abnormalities were those which at rest or after exercise showed unusual respiratory variations with good amplitude during inspiration [Brown (15), Grades I and II]. Tracings which showed marked abnormalities were those which at rest or after exercise showed notched J waves or low amplitude, irregular I-J waves which became unidentifiable in expiration [Brown (15), Grade III]. Tracings which showed maximum abnormalities included those with totally abnormal complexes of low amplitude under basal conditions (Brown (15), Grade IV). Mandelbaum & Mandelbaum (19), using the Dock ballistocardiograph, found this technique helpful in evaluating the recovery of the myocardium after coronary thrombosis. De Lalla, Epstein & Brown (20) studied the H waves of the ballistocardiograms of patients with complete heart block and atrial fibrillation. As H waves were seen without normal atrial contraction, it seemed probable that they represented a force produced at least in part by the apex thrust of the heart. Braunstein, Oekler & Gowdy (21) described a ballistocardiograph with two degrees of freedom corresponding to the frontal plane of the body.

Plethysmography was employed by Winsor (22), using the Burch pneumoplethysmograph, to describe the vasomotor reactions of the toe tip following arterial occlusion at the ankle for 15 min. In normal subjects, following release of arterial occlusion the relative rate of blood flow of the toe rose to a high level which was well above that of the resting flow, reaching its peak within 1 min. Among patients with arteriosclerosis obliterans, the relative rate of blood flow rose to a low level, slightly above that of the resting flow, reaching its peak in 3 or 4 min. This technique was suitable for measuring the arterial reserve in patients with peripheral vascular disease and as a means of selecting patients for lumbar sympathectomy since it could be carried out satisfactorily by a well-trained technician. Blood flow studies also were carried out by Mendlowitz (23), who employed the calorimetric method for measuring the blood flow of the finger tip He determined the vascular resistance of the finger tip of patients with polycythemia and hypertension. In polycythemia, the resistance was often increased before, and decreased after, phlebotomy. In well-established hypertension, resistance was increased. The relationship between pressure in the brachial artery and blood flow in the finger tip was found to be rectilinear

Electrokymography, originally described by Henny & Boone (24) in 1945, has found much clinical application in the past year. Schwedel, Samet & Mednick (25) stated that the electrokymogram was of aid in supporting the diagnosis of myocardial infarction in the presence of left bundle branch block where paradoxical pulsations of the left ventricle were present. Such [illegible]

progressive muscular dystrophy, angina pectoris, and certain subjects without heart disease. In patients with aortic insufficiency there was shortening or abolition of the isometric relaxation phase (the period preceding ventricu-

lar filling during which time the ventricle is a closed chamber and no volumetric changes are occurring). Ventricular hypertrophy without signs of congestive heart failure was associated with prolongation of the isometric relaxation phase which was one of the early signs of muscular fatigue. This phase was shortened by digitalis. Studies of the pulsations of the left atrium in normal and diseased hearts were made by McKinnon & Friedman (27). A characteristic abnormality of the electrokymogram observed in patients with organic mitral valvular insufficiency gave graphic evidence of regurgitation of blood from ventricle into atrium. *Electrokymographic evidence of* mitral regurgitation was found in certain persons with mitral stenosis who did not have an audible systolic murmur. Patients with Austin-Flint murmurs, and individuals with murmurs mimicking mitral insufficiency, showed normal atrial pulsations.

The Wolff-Parkinson-White syndrome was studied by Samet, Mednick & Schwedel (28) by recording simultaneously the electrocardiogram and the electrokymograms from the ascending aorta and pulmonary artery. Mechanical asynchronism was found in only 5 of 15 cases, but delay in ejection from both ventricles, regardless of the site of the bundle of Kent, was found in most instances. Dack, Paley & Brahms (29) also recognized a lack of significant asynchronism in right and left ventricular contraction in patients with Wolff-Parkinson-White syndrome. It was theorized that asynchronism did not occur because the early aberrant impulse traveled more slowly through the ventricular muscle than the normal impulse traveled through the His-Purkinje system. Thus, the premature excitation of the affected ventricle was offset by the slower propagation of the aberrant excitation wave Willis *et al.* (30) pointed out the importance of measurements of duration rather than amplitude and configuration in electrokymographic studies. Special attention was directed to the increased duration of the isometric relaxation phase which occurred in the presence of cardiac disease.

Vectorcardiography, originated by Mann (31) in 1920, has stimulated widespread interest and intensive study during the past year Grant & Estes (32), in a small book entitled *Spatial Vector Electrocardiography*, described a method for determining a spatial vector in which the various limb and precordial leads were treated as different perspectives or points of vantage in visualizing a three-dimensional electric field. They derived the spatial QRS vectorcardiogram from the standard leads and the precordial lead which showed equiphasic QRS complexes. The procedure was as follows: the frontal projection of the mean electric axis of the QRS complex ($\hat{A}$QRS)was derived from the standard leads 1 and 3 in the usual fashion; next, a plane passing through the body was visualized, the edge of which intersected the precordial lead and the center of which passed through the center of the heart at the origin of $\hat{A}$QRS; the vector and the plane were then adjusted, keeping the positions already determined intact, until they were perpendicular to each other. Thus the vector assumed a spatial position and the plane divided the body into its approximate electric fields.

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left bundle branch block it was inscribed in a clockwise direction with evidence of conduction delay. Scherlis & Grishman (39) stated that the spatial vectorcardiogram was of value in the diagnosis of posterior myocardial infarction as this condition produced a position of the spatial horizontal QRS loop which was more anterior than that encountered normally. Grant (40) studied a series of 80 electrocardiograms showing large S waves in the three standard leads, using the spatial vector method. It was found that when the QRS interval was 0.12 sec. or less, organic heart disease was not present and late depolarization in the right ventricle probably was responsible for the S waves in the limb leads. On the other hand, when the QRS interval exceeded 0.12 sec., left ventricular hypertrophy with or without left bundle branch block was present in nearly all cases. In no instance was cor pulmonale or right bundle branch block the etiology.

Electrocardiography

Various theories which are the basis of modern electrocardiography have been investigated experimentally in man and animals during the past year, and have withstood critical analysis.

Genesis of the electrocardiogram.—McGregor (41) studied the genesis of the electrocardiogram, in patients with tetralogy of Fallot having right ventricular hypertrophy, by comparing direct unipolar leads from an electrode on the pericardium, exposed during thoracotomy, with unipolar leads obtained from the surface of the chest. The anterior descending branch of the left coronary artery was considered the boundary line between the right and left ventricles. An rS pattern was obtained from the right ventricle similar to that derived from the left precordium. A qR pattern was obtained from the left ventricle similar to that obtained from the right precordium. These findings supported Kossman's (138) suggestion of almost complete reversal of the electric fields of the two ventricles in the thorax as a result of rotation of the heart.

Extrinsic interference in direct cardiac leads.—The question of extrinsic interference in direct cardiac leads was neatly answered experimentally by Kisch (42), who recorded simultaneously two direct leads from the exposed surfaces of hearts with slowly progessing contraction waves The electrodes were placed 5 to 20 mm. apart. Deflections of the base line registered by one electrode were not accompanied by a simultaneous deflection on the tracing recorded from the opposite side of the heart Thus, the author concluded that no interference of extrinsic voltages occurred in this study.

Conduction of the excitation wave in the atria.—Wenger, Hofman-Credner & Hortnagel (43) studied conduction of the excitation wave in the atria, using intra-atrial and esophageal leads. In patients with P mitrale, a local

electric axes of the P, QRS, and T waves in the frontal plane of the body. This was accomplished by recording standard leads 1, 2, and 3 and aVr, aVl, and aVf with normal polarity and with the polarity reversed. The 12 leads obtained were mounted in their appropriate positions on the hexagonal reference system. In this manner the direction but not the magnitude of the waves could be approximated by inspection. Grishman, Borun & Jaffe (34) described a technique for the simultaneous recording of the frontal, sagittal, and horizontal vectorcardiograms. The geometric arrangement selected for electrode placement was that of the cube. It was assumed that the origin of all electromotive forces generated by the heart was located at the intersection of a saggital plane passing to the left of the sternum, with a horizontal plane at the level of the fourth intercostal space midway between the front and back of the body. Electrodes were placed on four of the corners of the cube having this point as its center. Anatomically, the electrodes were placed posteriorly on the right shoulder and on the right and left lower thoracic regions, and anteriorly on the right lower thoracic region. They preferred this arrangement because there was a close correlation between the horizontal projection of the vector loop and the unipolar chest leads recorded at this level, because the heart was more nearly equidistant to the four electrodes at the apices of the cube, and because approximately the same anatomical structures were interposed between the origin of the action current and the surface of the body at the electrodes The authors stated that the QRS complexes of the unipolar thoracic leads could be derived accurately from the QRS loop of the horizontal plane, esophageal leads from the QRS loop of the saggital plane, and standard extremity and unipolar limb leads from the QRS loop of the frontal plane Cronvich *et al.* (35) described a simple electrode arrangement which permitted the recording of stereoscopic projections of the spatial vectorcardiogram, thus eliminating the need for constructing models to reveal the third-dimensional aspect.

Abildskov *et al.* (36) found that the spatial vectorcardiogram aided in the recognition of left ventricular hypertrophy in the presence of right bundle branch block In the frontal plane the portion of the QRS loop to the left of the isoelectric point moved in a counter-clockwise direction, was primarily directed toward the left, had a large open area, and was smooth and rounded in contour. The portion of the QRS loop situated to the right of the isoelectric point moved slowly during its inscription and was small and variable in area Scherlis, Lasser & Grishman (37, 38) showed that vectorcardiograms could distinguish between certain disease states which had similar conventional electrocardiograms. This was observed in right ventricular hypertrophy and in incomplete right bundle branch block In right ventricular hypertrophy, the horizontal QRS loop was inscribed in a clockwise direction without evidence of conduction delay. In incomplete right bundle branch block, the horizontal QRS loop often was inscribed in a counter-clockwise direction and showed conduction delay. Likewise in left ventricular hypertrophy and left bundle branch block the scalar electrocardiograms often

were similar; however, the spatial vectorcardiograms differed both in direction of inscription of the QRS loop and in evidence of conduction delay. In left ventricular hypertrophy the horizontal QRS loop was inscribed in a counter-clockwise direction without evidence of conduction delay, while in left bundle branch block it was inscribed in a clockwise direction with evidence of conduction delay. Scherlis & Grishman (39) stated that the spatial vectorcardiogram was of value in the diagnosis of posterior myocardial infarction as this condition produced a position of the spatial horizontal QRS loop which was more anterior than that encountered normally. Grant (40) studied a series of 80 electrocardiograms showing large S waves in the three standard leads, using the spatial vector method. It was found that when the QRS interval was 0.12 sec. or less, organic heart disease was not present and late depolarization in the right ventricle probably was responsible for the S waves in the limb leads. On the other hand, when the QRS interval exceeded 0.12 sec, left ventricular hypertrophy with or without left bundle branch block was present in nearly all cases. In no instance was cor pulmonale or right bundle branch block the etiology.

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delay of impulse conduction could be demonstrated in the left atrium, while the activation of the right atrium was completed in a normal fashion. Cases with P pulmonale did not reveal any abnormality of impulse propagation. In some cases in which the atrial intrinsicoid deflection was delayed near the midportion of the right atrium, a focal block within the right atrium was thought to be present.

Activation of the interventricular septum.—Sodi-Pallares *et al.* (44), in their study of activation of the interventricular septum of the dog, showed that the mean process of septal activation was from below upward and from left to right. The first region to be activated was on the left side and was between the apex and the base where the left bundle of His first branches. These findings are in accord with those of Burchell, Pruitt & Essex (45), who showed that, as a basic rule, the left side of the septum was activated early and the upper right side late.

Spread of the excitation wave through the ventricular myocardium.—Studies by Pruitt, Essex & Burchell (46) showed that the speed at which the excitatory process spreads through a segment of the myocardium depended upon the orientation of the fibers in that segment to each other and to the point of origin of the stimulus. Spread of the excitation wave down a strip of fibers in which the long axis of the fibers is parallel to the long axis of the strip is rapid. Spread of the stimulus down a strip in which the fibers run at right angles to the long axis of the strip is slow. Thus, endocardial activation is rapid because the subendocardium forms a network through which excitation can move rapidly along the long axis of the fibers. Spread across the interventricular septum, as in bundle branch block, and across the free wall of the left ventricle, as occurs in a normally activated heart, is slow because excitation is moving through fibers whose long axes are perpendicular to the advancing excitation wave.

Validity of the Einthoven triangle theory and the equilateral tetrahedron.—The validity of the Einthoven triangle was evaluated by Butterworth & Thorpe (47) by means of a double electrode cardiac catheter which was introduced into the human heart. Make-and-break shocks of low voltage were measured at the surface of the body with a string galvanometer. Calculation of the vectors of these currents indicated close conformity with the anatomic axis of the intra-cardiac electrodes The validity of the equilateral tetrahedron as a spatial reference system was studied by Abildskov, Burch & Cronvich (48) by means of an electric dipole placed within the esophagus Vectors plotted from the potential differences between electrodes defining the reference system were found to correspond fairly closely to the actual position of the dipole

Standardizing factors in electrocardiography—Cronvich, Conway & Burch (49) presented a method for determining the correction factors which are necessary in order to employ various reference frames, namely, the triangle, tetrahedron, or cube, whose boundary points represent electrode positions assumed to be equidistant electrically from the dipole of the heart. For ex-

ample, in recording the frontal plane vectorcardiogram, which is derived from standard lead I and VF, the sensitivities of the two galvanometers employed should be adjusted to 10 and 17 mm. per mv., respectively, in order to obtain agreement.

The ventricular gradient has received relatively little attention during the past year, probably because of the difficulties encountered in accurately measuring the areas of the waves. Johnston, McFee & Bryant (50), however, have described an electronic circuit capable of integrating the net areas of QRS complexes and T waves of the electrocardiogram, thereby simplifying the derivation of the ventricular gradient.

Unipolar extremity leads.—Leads of the electrocardiogram other than the standard limb and six precordial leads have been used during the past year with increasing frequency. Sokolow (51), in his study of unipolar extremity leads, concluded that they provided information over and above that obtained by the routine nine-lead electrocardiogram He stated that: (*a*) posterior myocardial infarction may be revealed by changes occurring only in lead aVf; (*b*) left ventricular hypertrophy may be revealed earliest by abnormalities in the left arm lead in horizontal hearts and by the left leg lead in vertical hearts; and (*c*) myocarditis may be revealed solely by changes in aVf.

Esophageal leads.—Oblath & Karpman (52), who studied esophageal leads among 40 normal subjects, pointed out that tracings recorded from the esophagus at the level of the ventricles closely resembled those from the left chest (V4, V5, V6). An esophageal electrode placed at atrial levels near the atrioventricular groove showed an intrinsicoid deflection of the P wave, a deep broad Q, and small R and inverted T waves Electrodes placed immediately behing the atria above the atrioventricular groove showed complexes similar to those seen in lead aVr. Using the esophageal lead technique, Hecht & Woodbury (53) studied the excitation of the human atrium by recording, simultaneously, tracings from the chest wall and the esophagus. They concluded that the mitral P waves of the standard leads and sharply biphasic P waves in V1 usually resulted from left atrial enlargement. Pulmonary P waves may be caused by abnormal cardiac rotation which allows the effects of both atria to be reflected backward and toward the left leg. Normal esophageal electrocardiograms were recorded by Kistin, Brill & Robb (54), who pointed out that the position of the atrial levels varied with the height of individuals. An atrial level was obtained at 40 cm. from the nares in most subjects of normal height. Scherlis *et al* (55) showed that esophageal leads taken from below the heart consistently reflected the electrocardiographic pattern of the diaphragmatic surface of the heart and resembled lead VF This was true in normal subjects and patients with myocardial infarction. The esophageal electrocardiogram was employed in the study of atrial activity and cardiac arrhythmias by Enselberg (56), who stated that probably the commonest application of esophageal electrocardiography will be in the differentiation of the tachycardias, especially in dif-

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normally. The findings of predominant positivity in esophageal electrocardiograms reflecting left ventricular cavity potentials served to differentiate incomplete or complete left bundle branch block from left ventricular hypertrophy.

Bronchial leads.—Bronchial leads, using the unipolar type of connections, were employed by Goldstein *et al.* (62) who inserted a No 4 French catheter electrode into the secondary branches of the bronchial tree as near as possible to the surface of the heart. Electrocardiograms were obtained from bronchi on the right, which resembled right atrial endocardiograms. Tracings recorded from bronchi on the left were similar to left ventricular epicardial, esophageal, or left precordial leads at the same level. When the bronchial electrode was placed higher in the bronchus, tracings similar to those recorded from the left ventricular cavity were obtained. No arrhythmias or serious reactions occurred during or after this procedure. Langner & Atkins (63), using intrabronchial leads on individuals without cardiac disease, studied the body as a homogeneous volume conductor. This was done by comparing the QRS complexes from tracings taken from within the bronchi with those taken from the surface of the body. The distribution of potential variations in the lungs, as manifested by the QRS complexes, corresponded approximately with the distribution of the QRS complexes recorded from the body surfaces. These findings support the validity of the Einthoven assumptions.

Endocardiography.—Endocardiography has been employed in many centers during the past year and much information has accumulated which confirms the principles already established by Dr. Frank Wilson. Little new or contradictory information has been added. Potential variations in the coronary venous system were studied by Levine & Goodale (64). Electric potentials were recorded from within the coronary sinus and the great cardiac vein of six individuals with normal hearts The ventricular complexes consisted of broad prominent Q waves followed by prominent R waves and inverted or biphasic T waves These tracings represented a composite effect of electric forces from the left atrium, ventricular cavity, and epicardium. Endocardiograms from the left ventricle were recorded by Zimmerman & Hellerstein (65) by retrograde catheterization of the ulnar artery. The intracavity potentials from the left ventricle were of the QS variety and confirmed Wilson's concept (139) of the earlier depolarization of the interventricular septum from left to right These workers were able to catheterize the left ventricle only in patients with aortic insufficiency of syphilitic origin; they failed in five normal subjects. Sodi-Pallares *et al* (66) recorded bipolar leads across the interventricular septum The left ventricle was catheterized by passing the catheter into the right radial artery The right side was preferred as there was less tendency for the catheter to pass into the descending aorta They found also that the left side of the interventricular septum was activated first. Right bundle branch block was studied by simultaneous unipolar endocardiograms from both ventricles by Steinberg *et al.* (67), who

ferentiating between atrial tachycardia and atrial flutter. This distinction is based upon the appearance of the P-R intervals which show an ascending base line in atrial flutter and exhibit intrinsicoid deflections in all atrial complexes. The appearance of the P waves in the esophageal electrocardiograms were remarkably distinct and uniform in all cases in which there was coordinated activity of the atria.

Retrograde conduction from premature ventricular contractions was studied by Kistin & Landowne (57) by means of esophageal electrocardiograms. The authors concluded that retrograde conduction to the atria from premature ventricular beats is common and that the theory of normal unidirectional block in the atrioventricular node is not tenable. Retrograde conduction often is not discernible in the standard leads, which explains why the phenomenon has previously been considered rare. Coronary insufficiency was studied by Scherlis *et al.* (58) in patients before and after exercies. Depressions of the RS-T segments recorded in precordial leads after exercise were associated with simultaneous elevations of these segments in the esophageal electrocardiogram taken at the level of the atria. These segment changes indicated widespread injury to the endocardial aspect of the left ventricle. Post-infarction intraventricular block was revealed by Burchell & Pruitt (59) by means of the esophageal electrocardiogram and was of value in the diagnosis of healed posterior myocardial infarction, particularly in the presence of right or left bundle branch block. The esophageal electrocardiographic finding typical of post-infarction intraventricular block is a wide R wave at atrial levels where a QR wave is usually seen. The intrinsicoid deflection of the QRS complex in the esophageal lead may be delayed as long as 0.12 sec. and a wide S wave may be present in leads 1 and V5. The authors postulated a lesion in the posterior apical myocardium which would delay the excitatory process in reaching the basal portion of the left ventri- [illegible]

the esophagus near the base of the left ventricle would be typically Q, wide R in configuration.

Complete left bundle branch block was studied with esophageal leads by Sandberg, Wener & Scherlis (60, 61), who pointed out that in certain cases normal conduction changed to left bundle branch block during increases in cardiac rate. In a patient, the left ventricular cavity potential was recorded by esophageal leads and showed a normal QS configuration when normal sinus rhythm was present. With an increase in cardiac rate, left bundle branch block was produced, which resulted in an equiphasic RS pattern in the esophageal lead. Incomplete left bundle branch block was studied in detail by the same authors. They stated that in normal conduction the posterobasal portion of the left ventricle was activated later than the anterolateral aspect of the left ventricle In incomplete left bundle branch block the posterobasal portion of the left ventricle was activated earlier than

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showed that there is an initial negativity in the potentials obtained from the left ventricular cavity in this condition. Left bundle branch block was studied with left ventricular cavity leads and esophageal leads by Wener, Scherlis & Sandberg (61), who showed that the left ventricular cavity potential was predominantly positive and consisted of equiphasic RS complexes with marked depression of the RS-T segments. A minute Q wave often preceded the RS pattern

Cardiac arrhythmias.—Various cardiac arrhythmias have been reinvestigated using special electrocardiographic leads and equipment in order to define their mechanisms more clearly. Prinzmetal *et al* (68) stated that in clinical atrial fibrillation the mechanical and electrical activities were similar to those observed in the experimentally produced arrhythmia. The motion of the fibrillating atria was visualized directly in high-speed colored cinematographs of the exposed hearts of human subjects during cardiac surgery and of experimental animals following the local application of aconitine or electrical stimulation. The presence of a chaotic, continuous, rapid, mechanical activity of an unusual type was observed and no circus movement was revealed. The P wave in rheumatic heart disease among patients with paroxysmal atrial fibrillation was studied by Masini, Comberiati & Puddu (69), who showed abnormalities of these waves between paroxysms of fibrillation in all of 45 patients studied Seventy-five per cent of the patients showed P waves greater than 0.11 sec. in duration. An increase in voltage and a characteristic contour of the P waves in the chest leads (diphasic in V1 and V2, upright and notched in V5 and V6) were encountered.

Atrial flutter with variable block was studied by Besoain-Santander, Pick & Langendorf (70), who explained the ventricular irregularity encountered on the basis of a conduction disturbance similar to that seen in sinus rhythm with second degree atrioventricular block of the Wenckebach type (progressive lengthening of the atrioventricular conduction time preceding a dropped beat) It was assumed that some of the nonconducted flutter impulses penetrated into the A-V junction and thus influenced the conduction of the subsequent flutter waves Herrmann & Hejtmancik (71) stated that digitalis was the drug of choice in the management of atrial flutter in patients with serious organic heart disease It usually acted by instituting atrial fibrillation which reverted to sinus rhythm on its withdrawal, particularly if quinidine was then given. The slow ventricular rate maintained by digitalis provided for adequate cardiac function. Quinidine sulfate alone was effective in restoring sinus rhythm in selected patients without grave organic heart disease, particularly if the flutter was of short duration. Frequently a 1:1 conduction was encountered with this drug, which produced a rapid ventricular rate

Ventricular tachycardia was studied by Armbrust & Levine (72) who

magnesium sulfate was at times helpful. Potassium salts or morphine were without effect.

Ventricular fibrillation due to digitalis preparations was studied by Enselberg, Croce & Lown (73). They re-emphasized the fact that bidirectional ventricular tachycardia often occurred before the onset of ventricular fibrillation. Only four cases of the latter due to digitalis have been reported to date. Two additional cases following intravenous administration of acetylstrophanthidin were reported by these authors. An important study on the mechanism of ventricular fibrillation was carried out by Scherf *et al* (74). In experiments on dogs, ventricular flutter and fibrillation were produced by topical application of aconitine to the surface of the ventricles Ventricular flutter was invariably stopped by cooling the area on which the aconitine had been applied. Ventricular fibrillation was neither stopped nor modified by local cooling. It was assumed that in ventricular flutter only one center forms rapid stimuli, while in ventricular fibrillation many centers are responsible for their production Various antidotes to ventricular fibrillation induced by mercurial diuretics were evaluated by Craver, Yonkman & Rennick (75), who injected certain diuretics into the jugular veins of dogs, thereby producing fatal ventricular fibrillation in the untreated animals. Among the antidotes studied, British antilewisite offered complete protection against the cardiac toxicity produced, and magnesium sulfate, atropine, and vagotomy offered weak protection. After ventricular fibrillation had become established, electric stimulation usually restored normal sinus rhythm, manual manipulation occasionally restored it, while ascorbic acid and acetylcholine failed.

Ventricular standstill resulting from the depression of the spontaneous rhythmic activity of different cardiac pacemakers (S-A and A-V node) by premature impulses was described by Pick, Langendorf & Katz (76). They felt that this mechanism was sometimes responsible for certain clinical cases with Morgagni-Adams-Stokes attacks

Bundle branch block.—Bundle branch block still remains the subject of numerous clinical, anatomic, and physiologic investigations. Sanabria (77) made microscopic studies of the entire conduction system of six cases with the electrocardiographic finding of bundle branch block. In no instance was an anatomic lesion present in the A-V node, junctional tissue, or bundles of His, but most cases showed evidence of disease of the left ventricle. It was suggested that the picture of left bundle branch block actually might be intraventricular block involving the ventricular myocardium rather than the bundle of His. The prognosis in bundle branch block of patients with coronary artery disease under medical care was shown by Johnson *et al* (78) to be three years. Among patients with hypertension it was 3 4 years and among those with heart disease of undetermined etiology, 3 6 years A similar study by Rodstein *et al.* (79) of a group of persons not under medical care at the time of the discovery of their lesion showed that bundle branch block was not commonly associated with demonstrable cardiovascular impairment,

and that the presence of bundle branch block alone did not imply high mortality in the absence of other major cardiac abnormalities. This is in keeping with the generally held concept that the etiology of the bundle branch block and the clinical evaluation of the patient are more important in determining the prognosis than is the presence of the bundle branch block itself. An outstanding study of bundle branch block was presented by Sodi-Pallares *et al.* (80) who clearly showed that the diagnosis of bundle branch block could be made in the presence of QRS complexes with durations of less than 0.1 sec. A large number of tracings suggestive of left ventricular hypertrophy were actually incomplete left bundle branch block. This diagnosis was made by the presence of slurring in the beginning of the ascending limb of R in those leads which reflected the potential of the left ventricle, most frequently leads 1, aVl, V5, and V6 Hein & Sanazaro (81) showed that paroxysmal bundle branch block could be reverted to normal conduction by vagal stimulation. The change in conduction was attributed to cardiac slowing rather than to any direct vagal action on the conducting system. Levy (82) described a case of left bundle branch block which converted to sinus rhythm with oxygen. Glushien & Goldblum (83) described an electrocardiogram with aberrant atrioventricular conduction with a P-R interval within normal limits and prolonged QRS complexes. The diagnosis of anomalous atrioventricular conduction was established on the basis of supraventricular premature contractions which were characterized by QRS complexes of normal width as compared with the wide QRS complexes associated with the basic rhythm. It was concluded that in aberrant atrioventricular conduction the P-R interval may be shorter than average but not beyond normal limits.

Exercise tolerance test.—Coronary insufficiency has been studied extensively by means of the exercise tolerance test. The widespread use of this test has materially reduced the number of unexpected deaths among patients who have recently had a normal electrocardiogram recorded at rest. The differentiation of S-T segment shifts associated with a rapid cardiac rate from shifts due to cornoary insufficiency was made by Littmann & Rodman (84), who recorded the electrocardiogram after exercise when the pulse rate had slowed to 100 beats per minute. They performed their test at the time of day when the patients customarily experienced angina. In many instances a constant cold stimulus was also applied. The test was not performed on patients with objective evidence of cardiac disease and no limit was set for the amount of exercise performed. This seems to be a practical point, as electrocardiographic changes typical of coronary insufficiency may be seen with as little as five sit-ups in certain patients with severe disease, or only after 300 or more jumps in patients with minimal disease. It is often necessary to adjust the amount of exercise to the patient rather than to try to suit the patient to a standard amount of exercise The relationship between the cardiac rate and the level of the RS-T segment was studied by Sjöstrand (85) in 70 normal subjects who had been given amyl nitrite or had been subjected to physical work. With a rising pulse rate, the RS-T segment tended to show a

slight elevation at first but later showed a pronounced depression. The pulse rate at which the RS-T level fell below the P-Q level in lead 2 varied between 70 and 135 beats per minute. The variations in electrocardiographic responses during exercise in normal subjects under unusually heavy stress were studied by Yu *et al.* (86), who showed that RS-T segment depression and changes in Q-T interval occurred in normal subjects if the stress imposed was sufficiently great. A large Q3 wave in otherwise normal electrocardiograms in normal subjects and patients with posterior myocardial infarction was evaluated by Shaffer & Chapman (87) using the exercise tolerance test. A positive test was obtained only in persons with myocardial infarction. Induced acute coronary insufficiency was studied by Chesky *et al.* (88) using the extremity and circumferential chest lead electrocardiograms. They concluded that the greatest RS-T segment depression after exercise occurred in the left unipolar precordial leads representing the maximum voltage of the R wave, usually in V4 or V5.

The effectiveness of khellin in nine patients with coronary insufficiency and angina pectoris was evaluated electrocardiographically by means of the exercise tolerance test by Best & Coe (89), who found that normalization of the tracing following the drug occurred in the majority of patients who previously had had abnormal tests. A beneficial effect was likewise noted on the symptoms with a reduction in the nitroglycerin requirement. The effect of oxygen and nitroglycerin on the S-T segment shifts induced by exercise was studied by Russek, Regan & Naegele (90), who showed that 100 per cent oxygen failed to prevent negative segment shifts, while nitroglycerin had a clear-cut prophylactic effect.

Myocardial injury and myocardial infarction.—Myocardial injury and myocardial infarction have been [illegible]

heart. Injury to the endocardium of the free wall of the left ventricle was produced and left epicardial ventricular leads were recorded. Depression of the RS-T segment resulted when the subendocardial injury involved the left ventricle only. These shifts disappeared almost completely when the same type of injury was extended into the septum. Posterior myocardial infarction was studied by Yu & Blake (92), who found that a significant Q wave was present in aVf in 91 per cent of patients with infarction and in 5.4 per cent of patients without infarction. It was suggested that in an adult the presence of a Q wave in aVf with a voltage of at least 25 per cent of the R wave and a duration of 0 04 sec or more usually indicated the presence of a posterior infarct.

Lateral myocardial infarction was studied by Levy *et al.* (93) who stated that typical tracings showed high R waves and shallow S waves in V1. These were due to an infarction which disturbed the normal electromotive forces of the free wall of the left ventricle, thus decreasing the depth of the S wave in this lead.

Misleading electrocardiographic abnormalities.—The QRS-T patterns which may be mistaken for myocardial infarction in the presence of left or right bundle branch block were studied in multiple precordial leads by Myers (94, 95). These cases were selected because there was subsequent exclusion of infarction in all cases at necropsy. Left bundle branch block was present in 4 of the 11 cases studied. The findings which led to an erroneous diagnosis during life were: (*a*) a triphasic qrS pattern in one or more of the precordial leads to the right of the transitional zone, (*b*) registration of an rS complex in lead V1 or V2 and a QS deflection in one or more leads farther to the left, (*c*) progressive diminution in the amplitude of the initial R wave, then replacement by a qRS deflection as the electrode was moved towards the left, and (*d*) cove-plane inversion of the T wave associated with QS or W-shaped complexes in leads near the transitional zone. Right bundle branch block was present in 7 of the 11 cases studied In none of these was a prominent Q wave in leads from the left precordium a sign of myocardial infarction. The same author also described certain QRS and T wave patterns suggestive of myocardial infarction in which myocardial infarction was excluded at necropsy and in which bundle branch block was not present The electrocardiographic abnormalities were actually referable to alterations of blood potassium, myocardial ischemia, subepicardial myocarditis, or to distortion from arrhythmia. Precipitous falls in blood potassium to low levels were manifested by RS-T depression and T wave inversions resembling those associated with acute subendocardial infarction Extreme hyperpotassemia caused marked widening of the terminal portion of the QRS complexes and fusion with the T waves to form a pattern that was at times mistaken for that of myocardial infarction complicated by bundle branch block Certain electrocardiographic patterns were associated with subepicardial myocarditis and pericarditis These showed: (*a*) localized elevation of the RS-T junction or cove-plane inversion of the T wave in the presence of an initial R wave of normal or low voltage, (*b*) abnormal upward displacement of the RS-T segment or cove-plane inversion of the T wave in complexes exhibiting a distinct Q wave and a normal Q/R ratio, or (*c*) localized reduction in the amplitude of the R wave in a given precordial lead below that seen in adjacent leads.

Peri-infarction block.—Peri-infarction block, an electrocardiographic abnormality resembling bundle branch block but usually associated with an old myocardial infarct, was described by First, Bayley & Bedford (96). The diagnostic criteria of this abnormality include· (*a*) evidence of infarction of the subendocardial region of the ventricular wall or transmural infarction with a circumferential region of subendocardial damage, (*b*) QRS complexes in the limb leads which are, or exceed, 0.11 sec in duration, and (*c*) a characteristic QRS pattern in the unipolar precordial and extremity leads More precisely, when the exploring electrode was placed over the center of a transmural infarct with a circumferential region of subendocardial damage, the associated ventricular deflections were of the QS type As the exploring elec-

trode was moved from the dead myocardium to the living injured muscle comprising the outer layer of the ventricular wall, there was late activation of this region and the electrocardiogram demonstrated an initial Q wave followed by a broad R wave, the downstroke (intrinsicoid deflection) of which terminated the long QRS interval. When the exploring electrode was placed directly over an infarction which involved only the subendocardial lamina, tracings of the latter type, namely, a Q wave with a broad R wave, were obtained. Electrode positions on the healthy ventricle across the chamber from a subendocardial infarction yielded QRS complexes characterized by an R wave which was followed by a broad S wave. The broad S wave indicated late activation of the blocked living muscle tissue surrounding the infarcted region. The magnitude of the R wave depended primarily upon forces from the uninvolved wall subjacent to the exploring electrode.

Ventricular hypertrophy.—Ventricular hypertrophy was studied by Goulder & Kissane (97) with the aid of augmented unipolar extremity leads. Of patients with left ventricular hypertrophy, 83 per cent had electrocardiograms which were characterized, in lead aVl, by an R wave greater than 10 mm with a T/R ratio less than 10 per cent, or by an R wave greater than 11 mm. A similar study by Schack, Rosenman & Katz (98) showed that left ventricular hypertrophy occurred in adults when R waves in aVl exceeded 12 mm. or R waves in aVf exceeded 19 mm. Criteria indicative of right ventricular hypertrophy included a final positive deflection in aVr greater than 4 mm. in adults and greater than 5 mm. in children over two years of age.

Congenital heart disease.—Congenital heart disease was studied by Paul, Myers & Campbell (99), who showed that the chief value of the electrocardiogram was in the diagnosis of ventricular preponderance, which was determined by means of the unipolar limb and multiple precordial leads. Atrial hypertrophy, encountered chiefly in association with pulmonic stenosis and tricuspid valve disease, could be detected best by the analysis of P waves in the right precordial leads, rather than in the limb leads. Intraventricular block was observed with atrial and ventricular septal defects, Ebstein's disease, and coarctation of the aorta. Gordon & Goldberg (100) correlated the right ventricular pressures taken during cardiac catheterization with the pattern of right ventricular preponderance in the electrocardiogram and found that a right ventricular preponderance in the electrocardiogram was always associated with an elevated right ventricular systolic pressure. Right ventricular systolic hypertension was present at times, however, when the electrocardiographic pattern of right ventricular preponderance did not exist.

Left ventricular aneurysm.—Left ventricular aneurysm was studied by Moyer & Hiller (101), who confirmed the finding of a persistent RS-T elevation as a diagnostic sign of this condition. This was explained by hypertrophy of the heart wall opposite the aneurysm or by lack of modifying potential from the infarcted myocardium. Ford & Levine (102) found microscopic evidence of a chronic inflammatory reaction in the pericardium over-

lying ventricular aneurysms in 7 of 10 patients. Thus, it was suggested that chronic pericarditis may be responsible for the persistent elevation of the S-T segments in certain patients with ventricular aneurysm.

Effect of potassium.—The effect of potassium on the electrocardiogram in dogs was studied by Bellet, Gazes & Steiger (103, 104), who showed that with hyperkaliemia the T waves may be elevated or depressed depending upon the state of the myocardium. The same authors showed that myocardial infarction did not gravely affect the tolerance of the dog to the intravenous administration of potassium chloride. That ectopic rhythms developing during potassium intoxication in man were escape mechanisms and were not the result of increased excitability of the myocardium was the conclusion reached by Levine, Merrill & Somerville (105). The early and preponderant effects of potassium intoxication were upon the subendocardial layers of the human ventricle, as shown by the elevated S-T segments in lead aVr and depressed segments in the percordial leads. Large U waves commonly were present in hyperkaliemia.

... *electrocardiogram*.—The pre-agonal electrocardiogram was ... found that, as death ap- ... then by ventricular extrasystoles ... rate. Terminally, ventricular complexes of the monophasic type occurred ... rdiac resuscitation was successful only prior to the appearance of the monophasic waves.

CORONARY ARTERIAL DISEASE

... ated with radioactive iodine by Freedberg *et al.* ... nal attacks ... ellate ganglion with ... ghteen patients had bilateral blocks performed with ... (buffered solution of ammonium sulfate). Complete relief of pain was obtained in 72 per cent with partial relief in 28 per cent of patients. There were no failures Reinjection was done on the average of three or four months The authors felt that this was a simple, quick, and effective method which had definite advantages over alcohol injections or surgical procedures. Angina pectoris was treated by ... including the anginal pathways, by ... ry relief of anginal pain resulted in all 10 patients in whom the ... th thoracic ganglia on the right and left were removed

Arteriolosclerosis of the coronary arteries was described by Jacobson & ... (110) in a patient in whom death was attributed primarily to arteri- ... characterized by involvement of ...

death are unlikely, while ...

Myocardial infarction has been studied from the anatomic, hemodynamic and chemical points of view with the result that the treatment of patients with this condition has been improved. Shock resulting from myocardial infarction was studied with Evan's blue dye (T1824) by Agress *et al.* (111), who stated that patients with a clearcut picture of peripheral circulatory failure had reduced blood volumes necessitating transfusion, in contrast to patients with congestive heart failure whose blood volumes were increased and in whom transfusions were contraindicated. Sodium and potassium retention in myocardial infarction was studied by Sampson *et al.* (112), who reported that in 15 of 21 cases of proven myocardial infarction the concentration and total excretion of sodium in the urine fell to levels below 30 m eq. per l. within three days after infarction despite a sodium intake which generally was maintained between 2 and 3 gm. daily. Evaluation of adrenal cortical activity suggested that myocardial infarction produced a stress phenomenon with an adrenal cortical effect on renal tubules resulting in sodium retention. The cardiac output (stroke and minute volume) was shown by Hauss & Koppermann (113) to decrease immediately following an attack of myocardial infarction. During the period of decreased output the arterial pressure was maintained by a rise of peripheral resistance. This change in the dynamics of the circulation lessened the work of the heart and represented a protective mechanism for the injured myocardium.

Anticoagulant therapy in the treatment of 920 cases of myocardial infarction showed a death rate of 11.9 per cent among those receiving this type of therapy as compared with 24 per cent who received no anticoagulant, in a study made by Smith, Keyes & Denham (114) The relief of chest pain by ethyl chloride spray in acute coronary thrombosis was described by Travell (115) who stated that within a few minutes after the application of ethyl chloride spray to the chest wall there was prompt relief of the intense pain of acute myocardial infarction in one patient. It was inferred that the stimulus for pain in acute infarction is of short duration but gives rise to a secondary, self-sustaining pain cycle which may be terminated by altering the flow of nerve impulses from the skin

Hypertension

Hypertension and hypertensive cardiovascular diseases were reviewed thoroughly and excellently by Corcoran *et al.* (116) A hormonal neurogenic vasopressor mechanism in dogs was described by Taylor, Page & Corcoran (117) which was dependent upon a vasopressor substance liberated into the blood as a result of vasostimulation. The substance was distinct from epinephrine, norepinephrine, renin, angiotonin, and pitressin. The phenomenon of hyperreactivity of arterial pressure to posture and cold was illustrated by Smithwick & Robertson (118) Twice as many hypertensive patients hyperreacted to the upright position and three times as many showed undue response to a cold stimulus as did the controls. Hypertension existed without hyperreactivity, but was the exception rather than the rule. The hypotensive

effect of high spinal anesthesia in hypertensive patients was shown by Pugh & Wyndham (119) to occur as a result of a decrease in the cardiac output secondary to venous hypotension which occurred probably as a result of sympathetic paralysis.

Subtotal bilateral adrenalectomy in the treatment of severe, otherwise intractable, hypertension was reported by Wolferth *et al.* (120). In five of the six cases in which removal of at least 95 per cent of adrenal tissue was combined with bilateral splanchnicectomy and bilateral sympathectomy (T-12 to L-2 inclusive), the early postoperative fall in pressure tended to be more satisfactory than that obtained from adrenalectomy alone. These findings suggested that effective control of hypertension by medical means may require the combination of depression of adrenal cortical function and interruption of sympathetic nervous system activity.

Total bilateral adrenalectomy in malignant hypertension and diabetes was reported by Green *et al.* (121), who described the course of a 28-year-old woman who improved after this operation. Evaluation of the patient 9 and 15 months postoperatively indicated that the progress of the renal lesions had been arrested, with an associated regression of the cerebral, retinal, myocardial, and vascular disturbances. The diabetes also was markedly improved and the insulin requirement was proportional to the amount of cortical extract administered

Adrenal cortical hyperactivity among patients with clinical signs of hyperadrenocorticism and hypertension was studied by Davies & Clark (122), who showed a definite decrease in sweat salt concentration as compared with other hypertensive patients and normal subjects. Adrenal cortical function in essential hypertension was studied by Eisenberg, Buie & Tobian (123). Sweat sodium concentrations in patients with mild or severe essential hypertension did not differ from that of normotensive subjects. This makes it unlikely that essential hypertension is related to increased adrenal cortical activity.

Pheochromocytoma.—Pheochromocytoma as a cause of hypertension has received considerable attention in the past 12 months Beyer *et al.* (124) showed that arterenol (norepinephrine) is the immediate precursor of epinephrine in the body, and that within the pheochromocytoma there is an impairment of the transmethylation reaction which is responsible for the conversion of arterenol to epinephrine. Goldenberg *et al.* (125) subjected 22 patients with pheochromocytoma to clinical analysis. Eighteen had persistent hypertension, and four had paroxysmal hypertension. When the tumor contained epinephrine predominantly or a large amount of arterenol, the clinical picture was characterized by hypertension, tachycardia, hyperhidrosis, hypermetabolism, and hyperglycemia Tests with benzodioxan (2-piperidylmethyl-1,4-benzodioxan; 933F) gave positive reactions When the tumor was small and contained arterenol primarily, the syndrome of essential hypertensive vascular disease was closely mimicked. The test with benzodioxan also gave positive reactions. Regardless of the pressor agent

found within these tumors, hypertension persisted for periods up to four weeks in 7 of 12 patients although all other clinical signs regressed promptly. This corroborates the view that excessive amounts of circulating catechols need not be present constantly to maintain an elevation in the arterial pressure. Pitcairn & Youmans (126) studied the nature of the pressor substances in pheochromocytoma. They comapred the effects of the tumor extracts of two patients upon the arterial pressures of dogs before and after the administration of the adrenergic blocking agent Dibenamine (N,N-dibenzyl-β-chloroethylamine). One tumor contained norepinephrine predominantly, and the other, an epinephrine-like substance, Dibenamine was similar to other adrenergic blocking agents in its inability to block consistently the pressor action of norepinephrine.

Cross, Lusignan & Pace (127) described the first case of malignant, metastasizing pheochromocytoma producing paroxysmal hypertension which has been reported in the literature. Calkins, Dana & Howard (128), studying current methods of diagnosis of pheochromocytoma, pointed out the value of laminograms in locating the tumor. One patient of seven in their series with paroxysmal hypertension due to pheochromocytoma showed a negative histamine test The benzodioxan test was particularly useful in the presence of sustained hypertension Nevertheless, it failed to produce a significant fall in the arterial pressure in two patients It correctly indicated the presence of pheochromocytomata in a total of 59 cases studied. Benzodioxan has not produced positive responses in patients in whom no tumor was found in this series.

A definite advance in the treatment of pheochromocytoma is in the use of the hydrochloride salt of Regitine [C-7337; 2-N-*p*-tolyl-N-(*m'*-oxyphenyl)-aminomethylimidazoline], an orally effective adrenolytic compound used by Iseri, Henderson & Derr (129), who reported that 25 mg per sq. m every 3 hr. orally was effective medication in an 8-year-old Negro boy. Physiologic studies in this case made on the extract of the tumor indicated that epinephrine was present in appreciable amounts Kositchek & Rabwin (130), studying arterenol and epinephrine, stated that arterenol is a primary amine differing from epinephrine only by the absence of an N-methyl group. Extracts of the adrenal medulla contained appreciable amounts of arterenol as well as epinephrine; therefore, the hormone of the adrenal medulla corresponds in its dual nature to these two known sympathetic mediators. Recent hemodynamic studies by means of right heart catheterization showed that epinephrine, within a physiologic range, acts as an over-all vasodilator and produces hypertension only by an increase of the cardiac output, while arterenol acts as an over-all vasoconstrictor with no change or slight decrease in cardiac output Holton (131) expressed his belief that because of its greater pressor activity arterenol is the probable cause of the attacks of high blood pressure

Dietotherapy.—Hypertensive encephalopathy associated with hypochloremia was described by Hilden (132), who reported five cases character-

ized by acute cerebral disturbances, hypertension, transient fall in plasma chlorides, and increases in blood urea. All patients had been on diets low in sodium. Improvement followed parenteral therapy with saline. Carefully controlled studies on dietotherapy of hypertension during the past year have shown convincingly that the level of the arterial pressure in certain patients with essential hypertension varies directly and to a clinically significant degree with the sodium intake. Corcoran, Taylor & Page (133) stated that roughly 25 per cent of patients with severe essential hypertension responded favorably to a prolonged restriction of sodium to 0.5 gm. daily. The rice diet was found to be in effect a simple low sodium diet. Dole *et al.* (134) stated that the best clinical responses to low sodium diets were among the benign hypertensive patients with good renal function. They believed that the beneficial effect obtained was from the adaptive responses induced by the limitation of sodium. Six patients with uncomplicated hypertension were treated with the rice-fruit diet of Kempner during a six-month residence in a metabolic ward. Five of the six showed objective clinical improvement as evidenced by significant reduction in mean arterial pressure, decrease in heart size, improvement in fundi, and return to normal of low or inverted T waves. Restriction of sodium but not of chloride appeared to be essential for the clinical effect. Adaptation proceeded slowly. Three months were required for attainment of steady weight by the smallest subjects. Dole *et al.* (135) showed that treatment with a low sodium diet (7 m eq. per day) caused significant reductions in the average arterial pressures of five patients with uncomplicated hypertension. These reductions were due to the limitation of sodium, since no arterial pressure changes were observed during a preliminary equilibration state of two to four months in which the low sodium diet was supplemented with salt tablets of 10 gm. per day. Weight losses and large variations in the intake of protein and of water during this time were without significant effect on the arterial pressure.

Dibenamine.—Dibenamine was used in patients with severe hypertension by Wunsch, Warnke & Myers (136), who administered 2 to 10 mg. per kg. by slow intravenous drip to 14 patients, 10 of whom had hypertension in the malignant phase A depression of supine arterial pressure was observed in every case, lasting from 1 hr. to several days and averaging 24.5 hr. The average maximum response of each patient was a drop of 59 mm. Hg systolic and 38 mm. Hg diastolic. The depression of the arterial pressure was greater and more prolonged than that produced by tetraethylammonium chloride. Orthostatic hypotension was demonstrable for as long as five to six days after the supine pressure had returned to the control level. Transient miosis, diuresis, and increase in urea clearance constituted other clinical effects.

Failure of surgery.—The causes of failure in the surgical treatment of hypertension were discussed by de Takats (137), who pointed out that irreversible renal disease was often a contributing factor. He described a water tolerance test which aided in revealing the presence of irreversible kidney

damage. The normal water tolerance was defined as the ability of the individual to concentrate the urine in 4 hr. and to eliminate most of the ingested water in the first 2 hr.

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DISEASES OF THE URINARY SYSTEM[1]

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The year 1950 to 1951 has seen the publication of a number of important reviews on renal function which are too long to be summarized, but which must be called to the attention of the student of renal disease. Homer Smith's book, *The Kidney. Structure and Function in Health and Disease* (1), reviews the subject of renal function and renal disease Although the practitioner will find rather brief descriptions of clinical entities and the natural history of the various renal diseases, there is a very valuable collection of data on functional abnormalities. Methods are critically examined. The great contributions of the functional method to our understanding of the mechanics of the kidney in health and disease are completely reviewed with references to an enormous bibliography.

A series of brief reviews of important subjects in renal physiology appeared in the *American Journal of Medicine* in the last year. Earle (2) wrote a brief, critical review of methods and of some of their limitations Pitts has reviewed the acid-base regulation by the kidneys (3). His studies indicate that the normal man can excrete 10 to 30 m eq of titratable acid per day, while 30 to 50 m eq. may be excreted by the mechanism of ammonia formation with neutralization of the acid. The ammonia mechanism is ordinarily about twice as effective as the acid excretion mechanism. In normal men, the output of ammonia is proportional to the acidity of the urine and also to the duration of acidosis up to about six days. The normal man can increase his ammonia production by a factor of 10. Maximal acidity and ammonia production are reached in the normal man at a plasma bicarbonate concentration below 20 millimoles per liter. When renal function is inadequate, the production of ammonia is affected even more adversely than the production of titratable acidity In the defense against alkalosis, the kidney operates as if there were a threshold for bicarbonate at 25 to 27 millimoles per liter This threshold is reduced by hyperventilation and is raised by deficiencies of chloride. These mechanisms of defense of the acid-base balance are apparently mediated by an ion-exchange mechanism in the renal tubule Berliner (4) has reviewed the renal excretion of water, sodium, chloride, potassium, calcium, and magnesium. He emphasizes the difficulty in the expression of tubular activity in the reabsorption of salt and water, especially in the presence of a system like the glomerulus and tubule, where tubular activity depends to a considerable extent on the glomerular filtration. The regulation of potassium excretion is carefully considered, and some of the difficulties in the interpretation are emphasized. As Berliner and others have

[1] The survey of the literature pertaining to this review was concluded in July, 1951.

demonstrated, potassium may be eliminated both by filtration and by tubular secretion. Ionic exchange is demonstrable when foreign anions are being excreted. Potassium excretion cannot be well correlated with the serum potassium or with glomerular filtration rate. Although the adrenal cortex plays an important role, the adaptation of the tubules is apparently even more effective than the action of hormones. It is at present still doubtful whether the linkage of potassium with chloride and bicarbonate excretion, pointed out by Darrow & Pratt (5), is due to renal or extrarenal factors. Some other important factors have been pointed out elsewhere by Berliner and his co-authors (6) The tendency for mercury to depress the secretion of potassium may be of importance when the kidney is laboring to excrete a high load. Potassium secretion may also be an important mechanism for the maintenance of a normal serum potassium in patients with chronic renal disease, as emphasized by Platt (7). The danger of a rise in the serum potassium in chronic renal disease has been emphasized by Farber (8), Merrill (9), McNaughton (10), and their co-workers. Further consideration of this subject will be made under the heading of treatment of anuria It should be remembered, however, that in chronic renal disease, especially in disease involving the tubules, in chronic acidosis, or in other circumstances which may precipitate potassium deficiency, a lowering of the serum potassium level may occur and may progress to the development of dangerous clinical symptoms, as pointed out by Davidsen *et al.* (11) and Schoch (12). This phenomenon offers another piece of evidence suggesting that the adaptability of the kidney in chronic renal disease is gravely reduced, with a resulting deviation of the internal environment under conditions either of an excess, or of a severe deficiency of a material normally excreted by the kidney. Another interesting sidelight on the interaction between renal function and potassium is noted in the report of Perkins and his co-workers (13). These authors remind us that animals on a low potassium diet develop myocardial and endocardial necrosis with replacement by scar tissue and infiltration with phagocytes Diffuse tubular nephritis is also seen, with edema, vacuolization, and sloughing of renal tubular epithelium. The authors report a patient with known potassium depletion who died after infusion of 10 per cent glucose solution. Lesions were observed in this patient's heart and kidneys which strongly suggested that they were related to potassium depletion.

The mechanisms for transport of substances across the tubular epithelium have been examined from a functional standpoint in the review by Taggart (14). In this type of transport, work is done against a concentration or potential difference, and a limited rate of movement is observed, often independent of plasma concentration and heavy load. The mechanics of the reabsorption of glucose, of other sugars, amino acids, creatine, urate, ascorbic acid, phosphate, and sulfate are examined Most of these substances show maximal tubular capacity for reabsorption, but there is some irregularity in the completeness of reabsorption Tubular excretory capacity can be examined with creatinine and potassium, but more accurate results are ob-

tained with the artificial substances, *p*-aminohippuric acid, iodopyracet-(Diodrast) injection, and certain dyes. Related substances may compete for a mechanism limiting the tubular maximum (Tm) for one substance in the presence of the other. An interesting and useful demonstration of this fact is exemplified by the studies of Burnell & Kirby (15) on the interference of *p*-(di-*n*-propylsulfamyl)-benzoic acid (Benemid) with the excretion of penicillin. Although maximal tubular excretory or reabsorptive capacity is ordinarily thought to be constant, it may be modified by the extirpation of some endocrine organs or by the replacement of their secretions. Taggart has examined further the biochemical aspects of renal tubular transport (16) and has been able to demonstrate the dependence of some of the transport mechanisms on recognized biochemical reactions within the cell.

Two recent reports by Oliver (17, 18) emphasize the morphological aspect of renal tubular secretion and reabsorption. Oliver points out clearly that the renal functionalist simply observes the entrance of materials into the kidney through the blood and their excretion in the urine and infers all of the intermediate mechanisms. The advantages of a morphological approach with further localization of the reaction and study of its progress under visual control are emphasized

Two recent studies confirm the normality of the response of the kidney in early diabetes Farber and his co-workers (19) demonstrate that the reabsorptive capacity for glucose is, if anything, increased in diabetes and tends to fall after treatment with insulin. Brodsky and his co-workers (20) have examined the diuresis caused by elevation of the blood sugar. They note that the diuresis of hyperglycemia is an ordinary osmotic diuresis comparable to that caused by mannitol or urea. In acute studies, they noted that such loss of water was accompanied by large losses of sodium chloride but that there was little increase in potassium or phosphorus elimination.

The participation of the kidneys in gout and in the excretion of uric acid have been examined in two reports. A recent combined clinic on gout includes a discussion of the excretion of uric acid. The maximal tubular reabsorptive capacity for serum levels occurs at very high levels, but uric acid escapes in moderate quantities well below this level of maximal reabsorption. Gouty patients with high uric acids therefore excrete more uric acid each day than do normals. Later in the disease, when renal damage occurs, the excretion of uric acid may fall (21). Brown & Mallory (22) have examined the kidneys of patients with gout from a pathological standpoint. All of these kidneys showed benign nephrosclerosis and deposits of urate in the

The interpretation of renal function must be modified in certain circumstances. Infants show considerably lower capacities in certain respects than do adults. Barnett (23) points out that infants fail to give good excretory pyelograms, that they excrete inulin and *p*-aminohippuric acid at relatively

lower rates, while the filtration fraction tends to be higher, and the excretion of sodium and the regulation of acidity are subnormal, as compared with adult standards. McCance (24) points out that the conservation of water is limited and that infants tend to respond less vigorously to the antidiuretic hormone. It is possible also to produce accumulation of water and of sodium under conditions of loading. When dehydration occurs, it appears to depress the glomerular filtration rate. The low level of excretion of phosphorus is a liability because of the decrease in the titratable acidity excretion which is involved. Babies, therefore, have to form more ammonia to balance the excretion of acid. Because the excretion of ammonia as well as other tubular functions may be lower in babies than in adults, acidosis occurs readily. In addition to the decreased capacity for the excretion of phosphorus, there may be a relative insufficiency of the parathyroid glands which stimulate the kidney to excrete phosphorus. Both of these factors may play a role in the development of hypocalcemic tetany in infants (25, 26).

McDonald and his co-workers (27) have shown that the declining renal function in older age groups is referable in part to a reduction in the renal blood flow. This reduction is reversible after the administration of pyrogen, with a return of several renal functions toward normal young adult levels.

Disorders of Fluid Balance and Diuresis

The importance of the regulatory functions of the kidney, as compared with its simple excretory function, has become evident during the past few years. One of the most striking disorders of regulation occurs in situations in which the general circulation of blood is impaired, with the accumulation of edema. The normal regulation of salt and water excretion is complex and fails to fit a simple description in terms of filtration and reabsorption (28). Borst (29), on clinical and experimental grounds, has divided diuresis into three clinically separable components. The first is inhibition of posterior pituitary function by an excess of water or by alcohol, while stimulation of the neurohypophysis leads to water retention under certain physiological or pharmacological stimuli. The second type of diuresis described by Borst concerns the output of sodium and water, which changes more slowly than the output of water alone. Borst believes that this is regulated by the cardiac output. It may be inhibited by fever and other stimuli The third type of variation in diuresis described by Borst is the diurnal rhythm of fluid excretion, which is reversed in patients with heart failure but is normal in patients with nephrosis. Borst attributes this difference to the orthopnea of cardiac failure and the upright position maintained by the cardiac patient, whose cycle returns to normal if he can lie absolutely recumbent for the 24-hr. period. While this classification of diuresis may be quite elementary, it may provide a starting point for the examination of the experimental evidence.

Brodsky & Rapoport (30) have examined the mechanism of polyuria of diabetes insipidus in man. They found the composition of the solutes normal during osmotic diuresis. Strauss (31) observed the effects of alcohol on elimi-

nation of water and electrolytes and found the effect compatible with a diminution in posterior pituitary function. Sinclair-Smith and his co-workers (32) have studied the effect of posterior pituitary extract on normal subjects and on patients with congestive heart failure. In neither group did the posterior pituitary affect the rate of glomerular filtration or of sodium or of chloride excretion. Holland (33) similarly found little effect of pitressin on sodium excretion in man after heavy loading with sodium chloride solution. Using hypotonic saline solution, Holland was able to induce edema and a fall of 10 m eq. per l. in the serum sodium concentration by the administration of vasopressin (Pitressin) injection. These studies make it unlikely that an antidiuretic hormone of the posterior pituitary type is the only event in the causation of sodium and chloride retention, such as that observed in cardiac failure. Nevertheless, antidiuretic substances have been repeatedly demonstrated in urine of patients with congestive heart failure and in other edematous states. Van Dyke has reviewed the difficulties in the current method for assay of antidiuretic factors (34). Using the technique recommended by van Dyke, Bercu and his co-workers (35) have shown that the dialyzed urine of patients with cardiac failure produces antidiuresis in trained, hydrated dogs. The substance involved is evidently not Pitressin, since commercial preparations of this hormone can be dialyzed through cellophane and would be lost under the conditions of the experiment. Such substances, which may stimulate the posterior pituitary to function but are not themselves the secretion of the posterior pituitary, are represented by the finding of an increased quantity of vasodepressor material in the blood of many patients with cardiac failure, studied by the method of Shorr (36). Shorr (37) has demonstrated that vasodepressor material is inactive when the stalk of the pituitary is cut, leading to diabetes insipidus.

Another clinically important antidiuretic mechanism which may be active in patients with low serum sodium concentrations has been emphasized by the recent studies of Leaf (38), Waterhouse (39), and their co-workers Both in experimental animals and in man a depletion of the extracellular fluid electrolyte leads to antidiuresis This may occur with low concentrations of sodium and chloride, even when edema is present The tendency of such low serum sodium concentrations to be persistent and to drift even lower in spite of the return of sodium to the diet has been confirmed by Squires & Elkinton (40).

The failure of salt and water excretion, attributed by Borst to circulatory deficiency, appears to depend upon several factors. It is unfortunate that the dog handles salt and water in quite a different way from man, since much experimental work using the dog must now be repeated. Wesson and his co-workers (41) have shown that a sustained expansion of extracellular fluid volume in the dog results in a large increase in glomerular filtration rate, which allows that animal to excrete salt with great rapidity. In man, however, Wiggins and his co-workers have demonstrated that the glomerular filtration rate changes very little, if at all, during the depletion or loading

with sodium chloride (42). These authors conclude that the decrease in tubular absorptive activity under salt-loading is more significant than the increase in filtration rate in raising the sodium output in man. Black, Platt & Stanbury (43) have demonstrated the importance of the tubules in the reabsorption of sodium in an elegant fashion. Five normal men were depleted of sodium and were then loaded with rapid infusions of hypertonic saline solution. A subnormal sodium output resulted, even when the tubular load was raised above the normal control level. These experiments should dissipate the illusion of a simple, fixed maximal tubular reabsorptive capacity for sodium which is operative in the physiological range in man. The adaptability of the renal tubular reabsorption of sodium may also be demonstrated in the dog when less vigorous conditions are imposed, as demonstrated by White, and by Blake and his co-workers (44, 45).

A recent exhaustive investigation of the nature of the renal circulatory changes in chronic congestive heart failure has been made by Grossman and his co-workers (46). They confirm the previously reported reduction in the renal plasma flow in heart failure. The elevation of the filtration fraction allows the maintenance of a relatively normal glomerular filtration rate in a certain number of such patients, however. Tubular function, as measured by the excretion of *p*-aminohippuric acid and the reabsorption of glucose, remains relatively normal, as does the completeness of extraction of excreted dyes. These authors conclude, as have others, that renal ischemia is the main factor. Fishman and his co-workers (47) have studied kidney function in cor pulmonale and conclude that anoxemia is not an important factor. A consideration of renal hemodynamics in congenital cyanotic heart disease by Scott & Elliott (48) indicates variability in different patients, but marked reduction in the glomerular filtration rate and in the oxygen saturation do not necessarily lead to salt and water retention.

These studies done under basal conditions do not necessarily reflect the natural course of events during ordinary life. Severe exercise, heat, or psychological stress may cause reduction in the renal blood flow (49, 50) Kattus and his co-workers (51) have studied the effect of milder exercise and have found no significant change in the clearance of creatinine, but a decreased excretion of sodium and chloride and a variable antidiuresis. Sinclair-Smith and his co-workers (52) studied a patient with heart failure with a relatively normal glomerular filtration rate. In such patients, sodium retention may occur on exercise with or without a reduction in the glomerular filtration rate.

In spite of the variability of the various formal renal functions in heart failure, there is no doubt of the importance of sodium and water retention in the precipitation of heart failure Friedberg (53) has emphasized the importance of the sodium intake in patients with anuria in the precipitation of cardiac failure Schroeder (54) and Platt (7) have emphasized that excretion of sodium and chloride may fall paradoxically when sodium chloride intake is increased in patients with heart disease. Rapid development of cardiac failure ensues. The retention of sodium and chloride during heart failure is

reversed during the improvement of cardiac function, while shifts of intracellular electrolytes and water may also occur, as demonstrated by Iseri and his co-workers (55).

Lombardo and his co-workers (56) have demonstrated that bleeding reduces the excretion of sodium and water by the kidney without necessarily changing the rate of glomerular filtration. Much less blood must be removed from the patient in the upright position in order to produce the same degree of salt and water retention than when the bleeding is done in the recumbent position. Congestion of the neck corrects the retention of salt and water after bleeding in the upright position. Welt & Orloff (57) have injected concentrated human albumin solutions to increase the plasma volume of normal subjects. Such injections of hypo-oncotic solutions of albumin produced a diuresis of water without change in creatinine clearance or increase in sodium or chloride output. More dilute solutions produced a more vigorous diuresis with some increase in the sodium output without change in the creatinine clearance. The rather minor effects produced in normal individuals are in striking contrast with the effects of albumin intravenously in certain patients with severe deficiencies of circulating albumin. Luetscher and his co-workers (58) found that in spite of losses of albumin in the urine and into the tissues, there was a rise in the osmotic pressure of the serum and a sharp expansion of plasma volume after injection of concentrated albumin into patients with nephrosis. Increased concentration of the plasma proteins appeared to depend on the elimination of the great excess of extracellular fluid which would otherwise simply dilute the injected albumin. An analysis of renal function after such injections (59) indicated that there was an increase in the glomerular filtration rate, an increased excretion of water, and a subsequent increase in the serum sodium concentration. About one-half of the patients then proceeded with a diuresis, associated with great quantities of sodium eliminated in the urine, but in other patients no sodium appeared in the urine and no diuresis ensued. Orloff, Welt & Stowe (60) studied similar patients, including one patient with a toxemia of pregnancy, after injections of concentrated albumin. Their results were similar, but they demonstrated little change in the clearance of creatinine, while they attributed much of the increase in urinary sodium to the rise in the concentration of sodium in the serum. Prolonged, heavy injections of concentrated albumin are probably undesirable in patients without albumin deficiency, since Gimbel and his co-workers (61) have demonstrated that congestive cardiac failure may occur.

The effect of elevation of the renal venous pressure on sodium excretion has been emphasized, but recent reports indicate that there is some variability and complexity in this tendency for sodium conservation when the venous pressure is elevated. Hwang and his co-workers (62) have shown that after the initial period of a few days, increased renal venous pressure is no longer effective, either in causing sodium retention or in the rather transitory changes in renal blood flow and glomerular filtration rate which may accompany the original rise in venous pressure. Farber, Alexander & Eichna

(63) have investigated this problem in man. The introduction of a balloon into the vena cava, resulting in congestion of the vena cava, including the renal vein, causes a transient fall in the glomerular filtration rate and renal plasma flow, but a progressive fall in water, sodium, and chloride excretion in a short-term experiment. These observers have made the important observation that congestion of the vena cava below the renal veins in man produces very similar effects, partly due to diversion of blood volume and extracellular fluid.

The effect of the adrenal in salt conservation is well known in Addison's disease, so that it is not surprising that attention has been turned to the adrenal cortex in situations in which an excessive quantity of sodium is retained, apparently by tubular reabsorption. Daughaday & MacBryde (64) have pointed out that there is no appreciable change in formaldehydogenic or 17-ketosteroids when maximal sodium conservation takes place associated with restriction of sodium intake. The administration of corticotropin (ACTH) in large doses produced salt retention with increased steroid excretion, but desoxycorticosterone had little effect on the steroid output. Locke and his co-workers (65) have studied the use of the sweat electrolyte composition and rate of sweating as an index of adrenocortical activity. These authors confirm the impression of previous investigators that the sweat sodium reflects adrenocortical activity or the administration of ACTH or desoxycorticosterone acetate, but they emphasize that dietary sodium chloride has an effect and that the auxiliary conditions, such as season, must be known in order to interpret a single result. Warming-Larsen & Wallace (66) studied the volume and composition of sweat during diuresis in patients with nephrosis They found that in the edematous phase of nephrosis the volume of sweat was reduced, the sodium concentration somewhat elevated, but the total sodium output was reduced When diuresis occurred after the use of ACTH or spontaneously, there was a return of the sweat volume and sodium to normal levels White, Gordon & Leiter (67) have studied the effect of congestive heart failure on the saliva electrolyte concentration, which appears to follow a pattern similar to that of sweat In heart failure there is less sodium and chloride in the saliva, while potassium concentration is higher than in normals on a normal diet. Reduction of the sodium content of the diet in the normal individual results in a lowering of the sodium chloride concentration of the saliva similar to that observed in cardiac failure, but patients with heart failure or normal sodium chloride intake still show the pathological reduction Deming & Luetscher (68) have attempted to assay the sodium-retaining activity of the corticoid fraction of urine. Increased sodium-retaining activity has been demonstrated in edematous patients with cardiac failure and nephrosis (68, 69). Changes in the excretion of such material after the administration of cortisone or of ACTH, correlated with the clinical changes in edema, suggest that adrenocortical activity may play a role in the variations in edema and other clinical manifestations of the nephrotic syndrome (70, 71)

Another important factor in the accumulation of edema is the antidiuresis and decreased sodium excretion which occur in the upright position. Lewis and his co-workers have demonstrated that the effect of the upright position can be counteracted in part by compression of the neck (72), suggesting that the effect is due to a reduction in pressure or volume of the fluids within the intracranial cavity. Epstein, Goodyer, and associates (73, 74) have shown that the antidiuresis of quiet standing is associated with variable changes in renal blood flow and glomerular filtration rate, and with a reduction in plasma volume. The intravenous infusion of albumin sustained the plasma volume but did not correct the other factors. Hypertonic saline, on the other hand, eliminated the antidiuresis but not the reduction in sodium output. It would appear that the antidiuresis and the reduction of sodium excretion are mediated by different factors.

The diurnal variations of renal function emphasized by Borst (29) have been further investigated by Baldwin, Sirota & Villareal (75) These authors note that in contrast with normals, who show reduction in kidney function during the night, six patients with heart failure and edema showed increased glomerular filtration rate, urine flow, and sodium excretion at night. A return of compensation of the cardiac failure resulted in a reversion to the normal type of diurnal variation.

It is important to keep in mind that many of these changes in renal and endocrine function are the result, not the cause, of the disease. These reactions, important and modifiable though they may be, are merely manifestations of the underlying disease and disappear when the fundamental physiological disturbance is remedied. A sound perspective in this setting is maintained by Burch & Ray (76) in their review of the mechanisms of congestive heart failure. Similar problems in the excretion of sodium occur in cirrhosis of the liver with ascites (77, 78).

Weston and his co-workers (79) have examined the effect of a very low sodium intake on renal hemodynamics in patients with hypertension. Reduction of the sodium intake to 20 to 35 m eq per day produced a reduction in glomerular filtration rate in five of the six patients examined The Kempner diet, with its very low sodium intake and inadequate nutritional composition, caused much more profound changes, with uniform reduction in glomerular filtration rate and in renal plasma flow, with a fall in the filtration fraction, and a reduction in tubular excretory function, as measured by the excretion of *p*-aminohippuric acid The injection of isotonic albumin solution increased the renal plasma flow without helping the reduction of filtration rate, while hypertonic saline tended to return the filtration rate and renal plasma flow to normal or above When impairment of renal function occurred there was a tendency for the serum concentrations of sodium and chloride to fall. The development of low serum sodium concentrations in heart failure under the stress of a severe sodium depletion regime is well known and is now being observed in other conditions in which a very low sodium diet is used, such as in hepatic cirrhosis (80, 81, 82) Variations in other electrolytes dur-

ing such periods of sodium depletion may also occur. Stock, Mudge & Nurnberg (83) have observed the development of hypochloremic alkalosis in the presence of sodium depletion. These authors found the effect of mercurial diuretics was highly variable, but in sensitive individuals a potassium deficiency could be precipitated. Kelly & Deming (84) have reported three patients in whom renal insufficiency associated with marked elevation of the serum potassium has occurred in edematous patients after a sodium-depletion regime with mechanical removal of body fluid. Nickel and his co-workers (85) have emphasized that in uremia sodium depletion occurs very readily and that a severe reduction of renal function may occur without obvious signs of dehydration or of low serum sodium concentration. These authors observed marked reductions in glomerular filtration rate and in other renal functions, with an increase in uremia, after brief periods of sodium depletion. These findings apparently depended on the failure of the severely damaged kidney to conserve sodium and chloride normally, but were not necessarily associated with reductions in the measured volume of body fluid.

Bright's Disease

The classification and nomenclature of Bright's disease still troubles many authors and leads to some confusion in definition. The division of cases of glomerular nephritis into Type 1 and Type 2 by Ellis is followed by some authors (86). Davson & Platt have examined this separation of cases and find that there is a considerable overlapping of pathology in the two classes (87). In general, however, it is possible to divide cases into those of abrupt onset and those of insidious onset, and the pathology appears to be somewhat different in the two types. Roscoe's analysis of biochemical and hematological changes in the two types of nephritis (88) follows the well-known pattern observed in acute glomerulonephritis, Type 1, and in the later degenerative and terminal stages of chronic glomerular nephritis, Type 2.

The classification of patients showing the characteristic features of the nephrotic syndrome also offers some problems in terminology and in interpretation. Oliver (18) has attacked the use of the word nephrosis, but no simpler term has been suggested Barness, Moll & Janeway (89) have reviewed the natural history of the nephrotic syndrome, while Metcoff, Kelsey & Janeway (90) have studied the interpretation of the functional changes. These authors have found the usual difficulty in differentiating between the [illegible]

logical process. Major (91) has reported a long-term follow-up of a group of five cases of so-called lipoid nephrosis in adults. These cases are either healed or nonprogressive after periods of 14 to 18 years. Heymann & Lund (92) remind us that the procedure introduced by Smadel & Farr for the production of experimental nephritis in rats with injections of antikidney serum, can produce lesions and physiological changes which resemble either a pure

or a mixed type of nephrosis in different animals. Some of these rats go on to a chronic renal insufficiency with hypertension and ultimate death, while others recover after a situation closely resembling the nephrotic syndrome. Rytand & Randall (93) point out that there is a difference in the immunological pattern of patients with acute glomerular nephritis as compared with patients with nephrosis. In acute glomerular nephritis the antistreptolysin titer, as has frequently been observed (94), is very high, while the heterophile antibody titer tends to be normal In patients with nephrosis, the picture is reversed, with high heterophile titers and low titers of antistreptolysin. Rytand & Randall attribute this, to some extent, to the age of the patient as well as to the characteristic disease Harris and his co-workers (94) also observed very high antistreptolysin titers in patients with acute glomerular nephritis and found that the antihyaluronidase titer ran parallel with the antistreptolysin titer Kelley, Good & Glick (95) have noted an increase also in the nonspecific hyaluronidase inhibitor of serum and in the serum mucoproteins after acute glomerular nephritis In nephrosis, on the other hand, they found increases in the hyaluronidase titer but a decrease in the serum mucoproteins. It seems somewhat doubtful that these variations in protein fractions of the blood can be accurately interpreted in the presence of such a sweeping disorder of protein metabolism and of serum proteins as occurs in the nephrotic syndrome

Further evidence that the immunological factors, although very important, may be difficult to interpret quantitatively is brought out in the report by Weinstein, Bachrach & Boyer (96). These authors observed 167 patients with scarlet fever who were treated with penicillin within 48 hr. of the onset of their acute streptococcal infection. Streptococci disappeared rapidly from the nasopharynx, and the antibody reaction was slight. In spite of this fact, rheumatic fever, as judged by laboratory evidence, developed in 7 per cent of the cases, while glomerular nephritis was observed in 3.5 per cent. One of the patients with glomerular nephritis showed characteristic clinical signs and azotemia All of these cases of glomerular nephritis recovered without sequellae The urine was clear during the interval between the streptococcal infection and the development of the nephritis It is evident that although the antistreptolysin titer is ordinarily higher in patients with acute glomerular nephritis than in ordinary forms of scarlet fever (94), these immunological reflections may be greatly modified by prompt treatment, but the secondary development of nephritis is not necessarily eliminated.

The effects of variations in adrenal activity on the renal lesion in Bright's disease will be reviewed in the subsequent section on these adrenal preparations It may be worthwhile to point out in passing, however, that in Cushing's syndrome one may see a clinical picture resembling that of nephritis with insidious onset (97) Weinberg and his co-workers (98) have also observed alterations in renal function with hematuria and proteinuria occurring during encephalography in man.

Bradley and his co-workers have reviewed the changes in renal function

occurring in various forms of renal disease. In acute glomerular nephritis (99) these authors observed a reduction in glomerular filtration rate as well as in various renal tubular functions, including the ability to extract *p*-aminohippuric acid from blood at the normal proportion. When the extraction of *p*-aminohippuric acid was taken into account, the renal plasma flow was found to be normal in many cases and commonly somewhat increased. The functional picture is interpreted as a pan-nephritis with variable degrees of vasoconstriction or hyperemia. Earle and his co-workers (100) have studied the relation between these changes in renal function and the electrolyte metabolism in acute glomerular nephritis. These authors have also found a marked reduction in glomerular filtration rate and in various tubular functions. The probable organic nature of the reduction in filtration rate is emphasized by the failure of the filtration fraction to rise with increasing blood pressure or heart failure. The authors conclude that renal function is not useful except perhaps statistically in the prognosis of acute glomerular nephritis. The reduction in glomerular filtration rate and renal blood flow probably plays some role in the electrolyte abnormalities with edema in acute glomerular nephritis, but there is no regular correlation. Hughes and his co-workers (101) have noted appreciable electroencephalographic findings in patients with acute nephritis. Of 24 children, 22 showed abnormalities.

In the nephrotic syndrome, with or without chronic glomerular nephritis, renal function is highly variable (90, 99). The glomerular filtration rate is usually lowered but has been observed to be quite high in rare instances in children Maximal tubular excretory function is reduced, and the ratio of renal blood flow to tubular capacity is uniformly increased. Such functional changes cannot be directly correlated with the clinical picture until severe reduction in function leads to beginning uremia. The functional nature of the reduction in glomerular filtration rate is indicated by the marked increases in filtration rate after the administration of concentrated human serum albumin to patients without advanced obliterative disease of the glomeruli (59, 99) Cizek & Zucker (102) found that hypoproteinemia per se failed to reduce the glomerular filtration rate in dogs after plasmapheresis These observations, together with the note that in humans with hypoproteinemia without obvious renal disease, the glomerular filtration rate tends to remain normal, indicate that the hypoproteinemia of the nephrotic syndrome is not the only cause of reduced filtration The observations of Kelley and his co-workers (104) indicate that the turnover rate of proteins in patients with nephrosis is greater than normal, as measured with labeled methionine. The authors are surprised at the rapid rate of turnover, suggesting that there may be maximal production because of the very low levels of the albumin in particular, but having some reservations about some unknown technical problem which may affect the method under these unusual conditions London has studied the half-life of cholesterol in the nephrotic syndrome and finds it longer than in the normal man (105).

The effect of the adrenal on the physiology of the nephrotic syndrome and

the use of the adrenal preparations in its treatment will be considered in a later section. The temporary relief of nephrotic edema by the injection of albumin is well known (58, 59, 99). Dextran has been suggested as a substitute for albumin (106). The observations suggest that replacement of the serum protein is not always effectual in returning the sodium and water balance to normal. Fox & Slobody have observed that persistent edema in nephrosis leads to changes in tissue composition (107). The accumulation of sodium, chloride, and water is most striking in muscles, while liver is little changed from normal in its composition. While cation exchange resins may be useful in the elimination of edema in patients with nephrosis, the hazards of their use, especially in the presence of any renal insufficiency, are impressive, requiring special care and chemical supervision (108, 109, 110). An interesting side effect of the use of ion exchange resins is the production of an increased number of urinary casts by the increased acidity associated with the use of resins in the hydrogen or ammonium form (111) In cases with massive edema, the use of Southey-Leech tubes may be highly effective and harmless (112).

The natural fluctuations in the course of nephrosis make the evaluation of therapy even more difficult. The list of infections which may be followed by diuresis is increased by the addition of a case of hepatitis, following which recovery occurred (113). The occurrence of remissions after heavy, prolonged use of sodium salicylate and sodium gentisate have been reported by Heymann and his co-workers (114). The important observations by Taylor, Corcoran & Page on the effect of nitrogen mustard on the nephrotic syndrome (115) indicate that diuresis and reduction of proteinuria may follow in an appreciable number of cases. The untoward actions of the nitrogen mustard on the gastrointestinal tract and on the bone marrow may prevent this treatment from becoming widely accepted.

The renal lesion associated with bacterial endocarditis requires immediate diagnosis and treatment. Villareal & Sokoloff (116) have shown that some of these patients come to autopsy undiagnosed because of a failure to study blood cultures intensively in suggestive cases The pathological renal lesions associated with subacute bacterial endocarditis are highly variable, ranging from predominant embolic destruction of the kidney to a glomerulonephritis, with a poor correlation between the extent of the lesion on histological examination and the renal insufficiency which is evident clinically. The importance of early treatment is emphasized by Gorlin, Favour & Emery (117) They find that the incidence of renal lesions has been greatly reduced by penicillin treatment and that in certain cases the renal lesion healed. However, three of their four patients with well-marked renal lesions after a late diagnosis failed to heal and went on to progression to renal insufficiency in spite of the treatment of the underlying infection. A curious form of renal lesion, usually not associated with clinical manifestations, has been observed in patients with chronic ulcerative colitis (118).

An increasing number of cases are now being recognized as having the

renal lesion of disseminated lupus erythematosus. Daugherty & Baggenstoss (119) have described seven cases with various manifestations of lupus erythematosus disseminata, including arthralgia, fever, a skin rash, elevated arterial pressure, cardiac murmurs, and anemia. All of these patients showed proteinuria and an abnormal urinary sediment. A certain proportion of cases develop the nephrotic syndrome. The disease ends in renal insufficiency in some cases, the course being rapidly downhill once definite nitrogen retention has developed.

As any renal disease progresses to destruction of renal tissue, marked reductions in all of the renal functions are observed. Differential diagnosis by observation of discrete renal functions is not always possible (99). However, the incidence of marked tubular dysfunction, as indicated by acidosis and base loss out of proportion to reduction in glomerular filtration rate, may indicate a disease affecting primarily the tubules From the standpoint of treatment, the recognition of the patient with salt-losing nephritis, or with chronic acidosis and base depletion, is extremely important, since these factors are easily remediable. The effective treatment of chronic renal insufficiency depends on the recognition of such physiological disturbances, and measures to improve them should be instituted. The effectiveness of the low protein diet in reducing the burden on the kidney is well recognized, especially in slowly progressive forms of renal insufficiency (120). The effect of dietary protein in increasing renal excretory work is theoretically probable, but the influence of this factor on the over-all oxygen consumption of the kidney and the total work is questionable (121, 122). Salvesen (123) has questioned the time-honored practice of blood transfusion in patients with chronic renal insufficiency. Although transfusion may lead to symptomatic improvement in the presence of severe anemia, it has no beneficial effect on renal function and, on the contrary, may precipitate renal insufficiency. Shorr & Carter's demonstration that aluminum gel strikingly reduced the renal load of phosphate (124) may have application in the treatment of chronic renal insufficiency as well as in the prevention of nephrolithiasis. The effect of an elevated phosphate concentration, of reduced calcium levels, and of acidosis on the formation of bone are well known. Follis (125) has challenged the concept that rickets (or osteomalacia) and osteitis fibrosa occur in distinctively different forms of renal disease Follis found these changes occurring singly or in combination in children with various forms of renal disease Further studies to correlate more exactly the pathological changes with the predominating physiological chemical disturbances are indicated. It is recognized also that hypercalcemia may affect the kidney function and ultimately may lead to destruction of renal tissue with extensive calcification. To the recognized causes, such as hyperparathyroidism and overdosage of vitamin D, Burnett and his co-workers (126) have added a syndrome of hypercalcemia without hypercalciuria or hypophosphatemia, with calcinosis and renal insufficiency, due to excessive intake of milk and alkali, such as may occur in patients with chronic peptic ulcer.

Continuing attempts to transplant kidneys to patients with chronic renal disease arouse some hope that with improving vascular surgery and increasing knowledge of immunological mechanisms, transplantation of the kidney may become feasible (127).

The tubular necrosis which follows a variety of conditions associated with reduction in renal blood flow and other injurious reactions, such as transfusion reaction, continues to receive the study deserved by a condition from which recovery is possible but which at present has a relatively high mortality. Bull and his co-workers (128) have made a detailed analysis of renal function in this condition. Their results indicate that the course of acute tubular necrosis can be divided into three stages: first, an anuric stage; second, the early diuretic phase in which tubular function is still much reduced; and third, the later stage with tubular recovery. In the first stage, when urine volume is below 300 cc per day, marked reduction in all renal functions was observed. Although the marked reduction in extraction of *p*-aminohippuric acid was compatible with Trueta's shunt mechanism, the finding of a relatively high arteriovenous oxygen difference makes such a shunt very unlikely. Similar findings and conclusions have been reached by Clark (129), Maxwell (130), and their co-workers. Bull emphasizes also the dangers of the early diuretic phase, when tubular function is still highly inadequate. Serious electrolyte loss may occur at this stage, and Bull records a case with a very low serum potassium. Complete recovery of renal function may take some months. Ariel & Miller (131) have studied the effects of abdominal surgery on the renal clearances and find that ordinarily there is no reduction in renal function When postoperative shock occurred; however, there were marked diminutions in renal function.

The treatment of the anuric patient requires strict withholding of water and of sodium chloride (53, 132) except in quantities sufficient to match the patient's losses, as well as a potassium-free intake of carbohydrate (134), a low protein intake, and appropriate antibiotic therapy. Although most clinicians follow such a conservative regime, there are certain complications which demand therapy If potassium intoxication occurs, it may be remedied to some extent by the use of a potassium-free ion-exchange resin in ammonium form, as used by Elkinton (135). Improvements in the technique of intestinal and peritoneal lavage have made these methods simpler and relatively effective (136, 137) The technique of the artificial kidney with dialysis of the blood outside of the body has also been continuously improved. Two recent reviews by Kolff (138) and Merrill (139) indicate that the procedure has become less formidable and dangerous, and that it has a definite place in the treatment of some patients.

Effects of Adrenal Cortical Hormones on Renal Function and Disease

The hormones of the anterior pituitary gland and of the adrenal cortex occupy a special place in a consideration of renal physiology and disease.

These hormones are apparently necessary for normal renal tubular function (4, 14). An excess may modify pre-existing lesions or may produce new lesions. A very brief and incomplete summary of experimental contributions to this subject will be made, followed by a summary of the data on the effects of the pituitary and adrenal hormones on normal renal function and in renal disease. Selye (140) has extended his observations on the effects of these hormones in large overdosage in the production of lesions of the vascular system and especially of the kidney of the rat. Desoxycorticosterone and the somatotropic hormone produce a deposition of hyaline or fibrinoid material in the walls of the arterioles and the renal glomeruli and lead to a fatal nephrosclerosis if high dosage is continued. Rats given cortisone or ACTH, on the other hand, develop glomerular hyperemia. It is interesting to note that the administration of cortisone or of ACTH corrects the vascular lesion of desoxycorticosterone in other organs, but not in the kidneys. These findings in rats are similar to those of Friedman and his co-workers (141), who found that cortisone also outweighs the effect of desoxycorticosterone at the renal tubule in terms of the excretion of electrolytes. Rich, Berthrong & Bennett (142) have noted similar lesions in the glomeruli after administration of cortisone to rabbits. They did not find such lesions when ACTH was given, in contrast to Selye's results in rats. Some discrepancies may be accounted for on the basis of different dosage, as well as species difference. All of these animals received very heavy doses of the respective steroids.

Another important function of these hormones on the kidney concerns the excretion of water and of electrolytes. Although the adrenocortical hormones are generally considered to retain fluid in the body because of their action on sodium excretion, there is also an opposing action in the increase in water output, as emphasized by Gaunt (143). The predominance of one or the other of these actions depends on the circumstances, including hydration, availability of water and of salt, endocrine function, and dosage of steroids Boss, Birnie & Gaunt (144) have noted that the diuretic effect of the adrenocortical steroids is primarily due to tubular activity, although some increase in glomerular filtration is observed when these substances are given to adrenalectomized animals.

Addis (145), Sellers (146), and co-workers have shown that adrenalectomy reduces the spontaneous or induced proteinuria observed in rats, while the replacement of a variety of adrenal steroids causes a return of proteinuria. Rich and his co-workers (147) have noted a striking lipemia, which can be produced in normal rabbits after the administration of cortisone.

The effects of cortisone and ACTH on experimental renal lesions produced by anaphylactic hypersensitivity have been studied by Rich and his co-workers (142) Although no appreciable change was noted in the positive skin test, there was a marked reduction in the glomerulitis as well as in the other vascular lesions observed in the control animal The animals receiving cortisone showed the glomerular dilatation already mentioned and a tendency to hemorrhage into the tubule. The comparable animals treated with

ACTH showed improvement in the renal lesion without the development of these manifestations attributed to cortisone Wedgewood, Hawn & Janeway (148) have noted a similar improvement in the glomerular lesion produced by hypersensitivity after the administration of ACTH. These workers started their injections of ACTH five days after the administration of the foreign protein in order not to interfere with antibody production, which appeared to follow its usual course in these animals. Knowlton (133), Hackel (149), and their co-workers found that ACTH and cortisone had no beneficial effect and possibly aggravated some of the evidences of the nephrotoxic nephritis produced by the injection of antikidney serum. Lippman & Marti (155) noted increased proteinuria and kidney weight when cortisone was given to rats receiving nephrotoxic globulin. These authors also found that in rats receiving only nephrotoxic globulin, the excretion of neutral reducing lipids was higher than in rats who received globulin from unimmunized rabbits, and that the level of reducing lipids could be correlated with the increases of proteinuria and of renal weight and with decreases in serum protein level and in renal function. These observations suggest that some exogenous or endogenous corticoids may aggravate this experimental renal lesion.

Burnett has shown that large doses of ACTH or cortisone produce some increases in renal plasma flow and glomerular filtration rate in normal men and have definite effects on some renal tubular mechanisms, including the ionic exchange of sodium and potassium (150). Kendrick and his co-workers (151) observed similar increases in inulin clearance. They did not observe any reduction in the maximal tubular reabsorptive capacity for glucose. The studies of Levitt & Bader (152) indicate that the effects of cortisone and ACTH on renal function may be transitory and may be related to the increases in extracellular volume which occur during the first two weeks of treatment. Rosenbaum and his co-workers (153) observed striking increases in creatinine clearance in normal men given large doses of cortisone. These patients also showed water diuresis (which could not be correlated with the changes in creatinine clearance), maintained their sensitivity to injected pitressin in spite of the polyuria, and showed a reversal of the normal rhythm of diuresis between day and night Lloyd and his co-workers (154) showed that adrenal cortical extract in large doses produced diuresis in patients in whom a marked reduction in the serum electrolyte concentration had been produced by administration of pitressin As has already been pointed out, the responses of premature infants are not always as adequate or even in the same direction as in the adult The responses of the kidney to adrenocortical secretions and to pitressin, in particular, are not the same as in the adult, as demonstrated by Klein (157) and Heller (158).

The use of ACTH and cortisone in the treatment of acute and subacute glomerular nephritis is occasionally followed by some improvement and sometimes by complications, but the consensus of observers is that the effects are too slight to be evaluated in a disease of such an irregular spontaneous course (159 to 163). Bad effects may be noted on the hypertension and

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Certain untoward effects may follow the administration of ACTH or cortisone to patients with the nephrotic syndrome. The accumulation of edema which occurs during the early days of treatment is usually of little importance, but it may be associated with striking hypotonicity of the extracellular fluid (70, 71, 166). A marked elevation of serum potassium may occur at this time and may lead to serious results unless treatment is discontinued (70, 166, 175). With the onset of diuresis during treatment with ACTH, a striking loss of potassium may ensue, with rapid fall in the serum potassium level (103). Children treated with large doses of ACTH or cortisone may develop hypertension with cerebral manifestations or may show rapid and widespread infection with a lowering of resistance (103, 166). These complications can usually be prevented or treated by appropriate changes in electrolyte intake and antibiotic therapy, but they may occasionally call for cessation of treatment.

In contrast to the effects of ACTH and cortisone in nephrosis, no beneficial effect on the renal lesion or nephrotic syndrome associated with lupus erythematosus or with diabetes mellitus is seen (160, 162, 176, 177). Holmes and his co-workers (177) observed some improvement in renal function in one patient, but the clinical effects were not striking. An elevated serum potassium level occurred in another patient, associated with striking hypotonicity, similar to that observed in the nephrotic syndrome. Proteinuria was generally unchanged or aggravated by treatment.

The use of ACTH or cortisone in the presence of chronic renal insufficiency is probably contraindicated in view of the undesirable metabolic effects. The long-range effect of treatment of chronic nephritis with the adrenocortical preparations remains to be evaluated. At the present time the chief indication appears to be the nephrotic syndrome, in which dramatic, temporary, clinical improvement occurs in a large proportion of cases. The associated improvement in renal excretory function offers some real hope that the gradual deterioration of renal function may be slowed or halted. The inflammatory process in the renal tissue is usually unaffected, to judge by the urinary sediment. Occasionally, however, a dramatic improvement in the urinary sediment may accompany clinical improvement. Such a change does not guarantee a persistent improvement, but an occasional sustained remission suggests that the activity of the renal lesion may have been halted.

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nitrogen retention when these are present. Rich (142) has stated that in view of the pathological effects produced by cortisone in rabbits with experimental nephritis, the use of this drug in acute glomerular nephritis is contraindicated.

In the nephrotic syndrome associated with glomerulonephritis or occurring without such evidences, the consensus of observers (160 to 171) is that ACTH is useful in producing a remission of clinical importance in a large proportion of the treated cases. Although there may be some exacerbations of the evidences of disease in the initial days of treatment, considerable clinical and laboratory improvement may occur during the second week of treatment or following the discontinuance of medication. Relief of edema has occurred in about two-thirds of the reported cases. This is frequently associated with a reduction in proteinuria and an improvement in the level of the serum proteins. Dosage and duration of treatment have not been established, but it would appear that the ordinary therapeutic doses of ACTH are effective, if given for more than one week. Recurrence of edema and response to repeated treatment have been observed. Most patients have been treated with brief courses of ACTH. The effects of maintenance therapy have not been adequately investigated. Striking physiological changes are observed during treatment, but the effects on the underlying disease remain uncertain. Striking increases in glomerular filtration rate and filtration fraction have been observed by Barnett (172), Metcoff (166), and their coworkers Although these are probably an important factor in the production of diuresis, they cannot be correlated exactly with the onset of sodium elimination (171). The abnormal excretion of sodium-retaining corticoids in the urine of patients with the nephrotic syndrome is reduced following treatment (68 to 71, 171). Increased excretion of 17-ketosteroids and 11-oxysteroids occurs during treatment with ACTH and is particularly striking when diuresis occurs (165, 168) Most observers have noted a decline in the elevated cholesterol concentration in many of the patients treated. Soshea (173), Emerson (174), and their co-workers have demonstrated an increase in the lipids during the first days of administration followed by a uniform decline in all of the lipid fractions, including phospholipids, during subsequent days of treatment.

Although there are many disagreements on the effectiveness of cortisone in the nephrotic syndrome, two large series have been reported with results similar to those obtained with ACTH (70, 175). Treatment of comparable [illegible]

[illegible] sone administration. Reduction of proteinuria may also occur during treatment with ACTH, while it usually follows the end of cortisone treatment. *Reduction in cholesterol* is more striking after the use of ACTH. ACTH usually results in a somewhat greater increase in the arterial pressure. Im- [illegible] aining activity [illegible] ministration of

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NUTRITION AND NUTRITIONAL DISEASES[1]

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I am as grateful as my predecessors for the principle established by Dr. Kahn and Dr. Stare that a review of this nature should not attempt to cover the whole field of nutritional work. This review deals with certain aspects of nutrition in the tropics, with kwashiorkor, and with the relationship of malnutritional disease in early life to disease in later life. There is inevitably some overlap with the review by Dr Meiklejohn and Dr. Passmore in the *Annual Review of Medicine* for 1951 (5) but the subject is covered from a different standpoint. No apology is made for re-emphasising the importance of kwashiorkor in Africa for a recent United Nations Food and Agriculture Organization (UNFAO) report (1) has concluded that "the amount and seriousness of kwashiorkor justify emergency action."

THE BACKGROUND OF TROPICAL MALNUTRITION

Any review of nutrition written in 1951 must refer to the publication of the long awaited reports on the Minnesota Experiment (2) and of the work of the Medical Research Council Unit established in Wuppertal in 1946 (3), reports which will doubtless take their place as classics in the literature of malnutrition All interested in malnutrition, and especially those who work where library facilities are inadequate, will be grateful to the authors for works which contain not only experimental details but also critical analyses of many aspects of the literature of malnutrition. Keys's work is a worthy companion to Jackson's classic volume, also emanating from Minnesota (4). The fact that two such studies of inanition and malnutrition, of famine and starvation, should come from Minneapolis, surely the centre of one of the best-fed regions of the world, is a curious paradox which underlines the tragedy of so much of the work on malnutrition Inanition and malnutrition have been under extensive study in some of the best-fed regions of the world, and this often under the impact of war, whereas in the badly nourished areas, and especially in the tropics, comparatively speaking, little has been done. Although the Minnesota experiment has been brought to a conclusion, and war has passed from devastated Europe, malnutrition, and indeed stark famine, are still rife in the tropics In the Minnesota experiments previously healthy and well-nourished men were subjected to a brief period of caloric undernutrition in which all the major components of the diet were reduced to approximately the same extent, and the mineral and vitamin requirements

[1] The survey of the literature pertaining to this review was concluded in July, 1951.

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with varying types of dietary deficiency from season to season and area to area This has been well brought out by the studies of Corkill (9, 10) in the Sudan where he had the opportunity, rare in the tropics, of repeating studies on the same people nearly 18 years later. In this area the population are millet eaters. They are constantly malnourished, on a diet deficient in animal protein, riboflavin, ascorbic acid, and other essentials. Their deficiency states ebb and flow with the seasons, being accentuated in the dry season when the scorching sun dries the herbage, reduces the milk yield, and forces the population almost exclusively onto a poor cereal diet. Over most of Africa, intake of animal proteins is usually low and there is a scarcity of livestock, because of trypanosomiasis, rinderpest, and other animal plagues, as well as overstocking on poor grazing land (11). Milk is scantily produced. Goats are common but their milk is little used. Pigs, new arrivals to most of Africa, can be kept, but religious scruples prevent consumption of either the meat or the products Fish is consumed where available but, as with other protein products, preservation and transportation are difficult, and it can only be consumed in the areas where it is caught.

The African is thus largely thrown onto the [illegible]

unfortunately laid too little stress on the protein content of food stuffs and have stressed the production of such foods as the drought-resistant cassava which has a low protein content. Poor communications hamper interchange of food products even in good seasons and prevent the speedy relief of shortages by rapid importation from elsewhere. The cost in any case could not be borne by the poor African peasant. He has scant provision for food preservation, and indeed such facilities are generally lacking, particularly for the preservation of foods rich in protein. Stored foodstuffs deteriorate rapidly in the tropics; vegetable staples may decay in a few days; cereal and leguminous seeds are a prey to insect pests. This problem can only be overcome by modern methods of storage. But it leads, in part, to the apparent thriftlessness and lack of foresight which is so common and so frequently deplored.

Poverty, ill health, malnutrition, and lack of adequate tools lead to the cultivation of barely sufficient food to keep the cultivators alive (11, 12) This aspect has attracted particular attention in the Gambia where it has been shown that in certain areas the work of each peasant cultivator, even if he worked to the limit of his capacity, could only produce enough for an average daily consumption throughout the year of 1,800 kcal per day. The consumption varied from 3,000 kcal. per day after the harvest, to about 1,400 kcal. per day in the "hungry months." The peasants were caught in a vicious circle which could only be broken by help from outside. Mechanisation of production led to an enormously increased yield The whole energies of these people were absorbed in growing enough food for themselves. No room

were adequate. The disturbing influences of extraneous disease were eliminated. The net result was only an approximation to the conditions usually met with in famines amongst communities that are usually well nourished (5) and bore little relationship to the conditions in Africa and in many other parts of the tropics. The complex problems of malnutrition, race, climate, and disease have been discussed in an extensive monograph by the Gillmans (6) to which frequent reference will be made in this review.

The differences between the American, European, and African publications emphasise the lack of contact between workers in tropical and temperate regions that has been a matter of growing concern in the last few years. Meyer (7) has briefly reviewed the evidence of lack of contact, a disharmony which has certainly been unfortunate for tropical medicine and may even have harmed temperate medicine. There are numerous reasons for this lack of harmony, especially the failure of tropical workers to define clearly the malnutritional states they encounter. This is due in part to the difficulty in disentangling the complicated threads of malnutrition and parasitism. But one cogent reason is that, despite the set-backs of a world war, there has been a steady improvement in the diet of most temperate dwellers, while contemporaneously the diet of the average tropical dweller has worsened, a process which is rapidly continuing in certain areas. Chatfield, Scott & Meyer (8) have calculated the changes in the amount of food available for the decade 1938 to 1948 for some 75 per cent of the world population. They have shown that the rate of population growth has outstripped the increase in food production with the result that there is a decrease of 6 to 7 per cent in the food available per capita. The main brunt of this deficiency has been borne by tropical dwellers, particularly in Asia, but also in Africa. As the disparity increases, the temperate physician becomes more interested in the problems of hyperalimentation and to him the bizarre and very complicated states of tropical malnutrition are quite unreal. The severity and the enormous scale of tropical malnutrition are becoming more and more clear In this review, written from an African standpoint, it is proposed to survey recent work on tropical malnutrition and on the consequences of malnutrition, and to compare observations made on experimental animals in temperate regions with studies of human disease in the tropics.

DIETS IN AFRICA

The duplication of acute or subacute human deficiency states in laboratory animals has provided a considerable part of the corpus of the literature of malnutrition. Short-term experiments, or experiments in which animals are maintained on a deficient diet at a uniform level for a long period, in no wise duplicate the common circumstances of tropical malnutrition Although acute episodes of deficiency do occur in the tropics, often on a devastating scale, they are merely superimposed on states of chronic malnutrition which may have existed since early childhood The state of malnutrition is not stable, nor necessarily progressive, but is liable to seasonal fluctuations

frequent in the main centres of population, and, as with appendicitis and gastric ulcers, it is seen in Africans who have, to a greater or lesser extent, adopted a European type of diet. During pregnancy there is no special supplementation of the diet, and domestic work and cultivation are continued till delivery. Indications of malnutrition (edema, anaemia, and signs of liver and cardiac insufficiency) are common, and abortions, threatened abortions, and premature delivery are very frequent. During pregnancy, excessive engorgement of the breasts, almost so marked as to resemble a suppurative mastitis, is not uncommonly seen. Lactation is profuse and may be long continued; Parkes (22) has recently surveyed the many reports on the ease with which lactation can be artificially induced in African women. Cases are recorded where grandmothers have suckled children (23); indeed one of the writer's African colleagues avers that he was suckled by his grandmother (24).

The Children

The birth weights of African children are only known for relatively small groups; in Uganda (25), the average in some places compares not unfavourably with that of European babies, but in the Congo the weights are 400 to *500 gm. lower (17), and this is probably more generally true. Dean (26)* studied the birth weights of children born in Wuppertal (Germany) during a period of acute food scarcity and found that the weights were 150 gm. lower than in times of plenty. There is no reason to suppose that racial factors or prematurity are responsible for the low birth weights recorded by Lambillon. They are probably the result of maternal malnutrition which, from the work of Dean, would appear to be of a very severe degree. The birth weight is of importance in the development of the child, for, as Illingworth *et al* (27) and Parfitt (28) have shown, the children of the lowest birth weight remain the smallest children. Such low-weight African children are born with a legacy of somatic and biochemical defect which places them at a considerable disadvantage as compared with children of higher birth weights (6, 29). The incidence of congenital abnormalities among African children is not known, but certainly some congenital lesions, such as harelip, cleft palate, and congenital heart disease, are less commonly seen than in Europeans (30), but others, particularly those affecting the bones, may be more common (6) Carter (31) has recently studied a large group of infants in England and could find no evidence to suggest that maternal mlanutrition played any part in the etiology of the malformations he encountered. But, in view of the growing experimental evidence for the production of deformities in the offspring of animals by maternal malnutrition, and of the poverty of the nutrition of African mothers, the possible association in humans should be further investigated.

Breast Feeding

The African infant enters a particularly dangerous world where only the fittest can hope to survive. The conditions of breast feeding have recently

was left for the growing of cash crops or for other enterprises which might increase the communal wealth.

Bascom (13) has studied the diet of the Yoruba people of West Africa, which is based on a sedentary hoe agriculture, and has pointed out that, as elsewhere in Africa, the diet is overwhelmingly carbohydrate in nature; meat is rarely eaten by the ordinary man, and fresh fruits are little consumed Food is boiled or fried in vegetable oils in earthenware pots and highly seasoned with peppers. Roberts (14), writing of African school children in Kenya, says,

> they live with their parents and partake of the ordinary diet common to the reserve —mainly white maize, unripe bananas, potatoes and some beans—this being the mainstay of their principal meal of the day which is eaten in the evening. Gruel made mostly from maize and water, but sometimes from millet, is taken in the morning about 7 a m. and this has to sustain them till the evening meal. No milk is given after weaning.

Where milk is available it is usually diverted to the adults, to the breadwinner, as a luxury food. The idea that children, and pregnant and lactating women, need extra food is largely foreign to the African conception.

With the necessary and inevitable industrialisation of the tropics, the situation, as Stransky and Dauis-Lawas (15) point out, will deteriorate. The diet of the town-dweller, cut off by the high prices from eggs and dairy products, and with his staple foodstuffs often scarce and therefore more expensive, is often worse than that of his rural compatriots.

The Mother

Important studies of African women have recently been reported from the Belgian Congo by Drumel (16) and by Lambillon (17, 18). In opposition to popular ideas, Drumel, following Bartholemi (19), is in agreement with Kark (20) and with Ellis (21) that puberty is delayed in African girls as compared with Europeans, and though Lambillon (17) disputes this, he agrees that it develops more slowly and irregularly. Drumel (16) has evidence that the menstrual cycle is governed by a relative excess of estrogen and a deficiency of progestin, an imbalance which it is suggested is largely responsible for the high incidence of amenorrhea, cystic glandular hyperplasia, infertility, abortions, and prematurity. This is believed to account, at least in part, for the decrease in population in many areas of the Congo. The menopause occurs earlier than in European women. The pelvis is round, the musculature of the pelvis and of the abdominal wall is weak, and prolapse is common. The cervix is rigid and does not easily dilate, relaxation of the pelvic ligaments is poor, and at Caesarean sections remarkable thinning of the lower segment is seen which, with the rigidity of the cervix, conduces to frequent ruptures of the uterus. On the other hand, despite malnutrition and endocrine imbalance, eclampsia and other toxaemias of pregnancy are rare. Before 1937 eclampsia was very rare, but it is becoming more and more

contain vegetable fats and, rarely, meat or fish: such stews often contain mucilaginous products and condiments, the latter being sometimes present to an excessive amount (1). The food is often stuffed into the child in large quantities, the more so as the child's condition deteriorates. As Housden (32) says, "Malnutrition and overfeeding go hand in hand."

KWASHIORKOR

It is under such conditions that kwashiorkor arises, a disease well recognised by the Africans themselves. The disease has recently been reviewed by Meiklejohn & Passmore (5), by Davies (40) from Africa, by Stransky & Dauis-Lawas (15) from the Philippines, Indonesia, and South China, by Manson-Bahr (41) from Fiji, by Thomson (42) from Malaya, and many aspects have been exhaustively discussed by the Gillmans (6). Reports on the seriousness and prevalence of the disease led the World Health Organisation (W.H O.) and the Food and Agriculture Organisation (F.A.O) to appoint a team to make a survey in Africa; this was carried out by Brock & Autret and a detailed report has been published (1). It is no exaggeration to say that it is probably the most widespread of malnutritional diseases today and probably the most serious Its nature, importance, and indeed its very existence, have been obscured by many factors: firstly, by the fog of parasitic infestation which still beclouds so much of tropical pathology; secondly, by its widespread prevalence which, at least in Africa, has made it seem part of the natural order of events; a phase of childhood, just as rickets was once so regarded in western Europe; thirdly, by the focussing of undue attention upon certain inconstant skin changes with the result that there was a refusal to recognise the disease when these particular changes did not occur; fourthly, by its unfortunate identification with pellagra, a mistake for which the lack of precise definition was responsible.

Definition of Kwashiorkor

Brock & Autret (1) thus defined it:

> Kwashiorkor Syndrome—a nutritional syndrome occurring particularly in the age period six months to five years among indigenous Africans in places where foods rich in animal and other first class proteins are not customarily used in the feeding of children during the weaning and postweaning periods

They recognised that, in their definition, they had imposed a strict geographical localisation of the disease, but this was because their survey was confined to Africa and because, as they pointed out, the term "kwashiorkor" was etymologically linked with a particular type of pigment alteration which might not be present or take the same form in other continents. They considered the many other names which have been applied to the disease in Africa and preferred the name "kwashiorkor," a name which has now such standing in the literature that it may well continue to be used for cases outside Africa, for it is certainly shorter than some of the polysyllabic terms sug-

been under study in several areas of Africa. Housden (32) has described the situation in northeast Africa. Here, as elsewhere, breast feeding continues for two, three, or four years. During the first nine months, the mother usually takes only watery gruels and simsim oil. In few areas is any supplemental feeding given to nursing mothers, and where any is given, it is almost entirely starchy in nature (1) The time supplementation starts, and the exact type of food given, vary from place to place, but in almost all areas the supplements consist only of watery gruels or sweet foods like the banana. There is little conception anywhere in Africa that a child needs specially prepared foods in the postweaning period, or more frequent meals than an adult. A substitute for the former is afforded by the mother's chewing the food and then ejecting it directly into the child's mouth, a practice commonly used in Europe until the sixteenth century (33). The African compromise is to prolong breast feeding into the second or third year, and to add parts of the two daily meals of the parents, to enable the child to survive.

The milk produced by African women has not yet been exhaustively *analysed, but it is known to show an abnormal fat-protein ratio. In comparison* with European figures, the protein content over the first nine months of lactation are not vastly different, but African breast milk contains a considerable excess of fat (1). Analyses of African human milk by Auffret & Tanguy (34) have shown a lower level of methionine (mean 16 4 mg. per l) as compared with Europeans (mean 97 0 mg. per l). They quote studies which show that the cystine content is also low There is little doubt that, as breast feeding continues, both the quality and the quantity fall off. Platt (35) has found in the Gambia that the amount of milk that an infant from 12 to 18 months old could obtain from the breast averaged about 28 ml per hr., an amount clearly insufficient for the child (36, 37).

Yet it is striking how, in many areas, the infants do well in early life, gaining weight for the first few months at much the same rate as a European child. Detailed studies have shown that the weight curve begins to drop below the European figures at about the sixth month (38), though in some areas this is noticeable at the fourth month, and in others not till the ninth month. It has not caught up the European figures by the end of the fifth year Brou (39) reports from the Congo that the children at 36 months are often as much as 1100 gm. below European levels. As this increasing weight disparity becomes more and more marked, it may happen that the child is displaced from the breast by its successor. In many tribes sexual intercourse is prohibited during lactation, but this is not so in all areas The new child displaces its senior, and lactation continues so that the mother may be lactating continually for many months. On weaning, the watery gruels may be continued, and the child passes onto an adult diet, watered down in some instances, without the gradual progression through selected foods which is customary in more favoured countries The diet of the weanling thus consists basically of the watered-down local form of carbohydrate, possibly prechewed by the mother, and stews of varying composition, which usually

clusion has been reached that in hunger edema there is no close association, at least in the hunger edema seen in Europe during and following the late war (2). It was claimed that the edema was due to the persistence of a normal quantity (2) or an increased quantity (3) of tissue fluid in an emaciated body, there being disproportionate wasting of the body tissue without "wasting" of the fluid. The presence of hypoproteinaemia did not correlate closely with the edema. In kwashiorkor with edema, there seems to be extremely close correlation between hypoalbuminaemia and edema. "Hunger edema" may not be a single entity as recent work has suggested, but may be of at least two different types, and the predominance of one or the other depends upon the gate, of which there are many, by which the patient enters the field of malnutrition.

As in all nutritional deficiencies, attention was first directed to the most advanced cases, the few or many who cluster at the apex of a vast pyramid of malnutrition. The widespread occurrence of lesser manifestations of a particular deficiency are recognised later. This is true of kwashiorkor where the advanced cases in the florid stage all show edema, hypoalbuminaemia, and weight loss If the edema is due to the hypoalbuminaemia, then there should be a vast number of cases of hypoalbuminaemia who have not reached an edematous level, and who will show only weight loss and possibly other signs. Now, from the studies quoted, we know that weight loss in the late stages of breast feeding is almost invariable in African children There is as yet no evidence that hypoalbuminaemia is also very frequent. The frequency of advanced cases of kwashiorkor might therefore be a manifestation of malnutrition on an enormous scale, probably affecting the great majority of [illegible]

then rises rapidly to its peak in the second year to fall slowly in the third or fourth years to negligible proportions (52). The peculiar age incidence of severe kwashiorkor has yet to be explained. The disease is not seen in the second rapid growth phase at puberty.

Gastrointestinal disorders.—Gastrointestinal disorders are extremely frequent, being present to a greater or lesser extent in practically every case. Diarrhea is common. It is often mild, but may be very severe and intractable, and is often aggravated by the common custom of giving enemas to young children, and the application of irritating condiments to either end of the gastrointestinal tract. Brock & Autret (1) refer to the belief in some areas that if small children pass less than three to five motions a day they are considered constipated and given an enema:

> . which is administered in a picturesque way by means of a long pear shaped gourd with a hole at either end The most pointed end of the gourd is introduced into the [illegible]

irritating by the inclusion of red pepper.

gested. In this case the words "among indigenous Africans" should be expunged from their definition.

Brock & Autret (1) defined and discussed the fundamental characteristics of the disease which include: (*a*) retardation of growth in the late breast feeding, weaning and post weaning periods; (*b*) alteration in the texture and pigmentation of the hair, and to a lesser extent the skin, for which they suggest the term "dyspigmentation"; (*c*) edema, usually associated with hypoalbuminaemia; (*d*) gastrointestinal disorders; (*e*) nutritional dermatoses, occurring in a variety of patterns (occasionally no dermatosis is present); (*f*) peevishness and mental apathy; (*g*) anaemia; (*h*) atrophy of the pancreatic acini with decline in the enzymic activity of the duodenal contents; (*i*) pathologic changes in the liver which include one or more of the following: fat infiltration, necrosis, fibrosis; (*j*) a high mortality in untreated or incorrectly treated cases.

Clinical Findings

Of these changes, retardation of growth is probably constant although, despite this retardation, the infant may not in the early or florid stage appear wasted, but may show the plumpness of edema and often a considerable layer of subcutaneous fat. At necropsy, this fat layer may be a centimetre or more thick over the abdomen (40), and it was its presence which misled many workers into the belief that the condition could not be due to malnutrition. If the diet is adjusted and the edema disappears, the gross wasting of the muscles is apparent (43). If the disease progresses, with continuing failure to digest food, then the child passes into a marasmic state with gross emaciation (15, 44). The growth retardation affects weight more than stature.

All reports from Africa and elsewhere agree that there is very great reduction in the serum albumin, and this again would appear to be a fundamental lesion. There is a very close, and possibly an invariable, association of edema with the hypoalbuminaemia (45). The edema may arise primarily in any part of the body, but usually it soon becomes generalised. Estimation of the total serum proteins is sometimes misleading, since with the hypoalbuminaemia there is frequently a hyperglobulinaemia which may be of an extreme degree (46). The α- and β-globulins are little altered, the rise being mainly caused by an increase in the γ-globulin. This rise in the gamma globulin is not due to infestation with tropical parasites, as it occurs to an equal [illegible]

with an increased, but usually with a decreased, serum albumin (47, 48). Symul (49) has shown that the serum protein pattern in the newborn African children is normal and that these changes are not due to race or climate.

The association, or lack of association, between hypoalbuminaemia and edema (50) has been the subject of much study in recent years, and the con-

Severe kwashiorkor can certainly occur while the hair is of normal colour and there is no close correlation between the degree of dyspigmentation and the severity of the clinical state (53). Since, even in Negroes, there can be very much variation in skin colour, whereas the hair is almost always jet black, dyspigmentation of the hair is a more reliable sign than a dubious change in skin colour. The changes in skin and hair must thus be distinguished from genetic variations in colour and texture Brock & Autret conclude that when the hair is altered in texture and in colour, this change is associated with protein deficiency, and that alteration in hair colour to a reddish hue without changes in texture is probably due to malnutrition. Much more study of the hair changes is required, but it is interesting that these changes are recognised, by both Africans and Indonesians, as caused by malnutrition, and they recognise that on good feeding the hair will revert to normal. Thus although the hair colour changes may not be seen in all races which suffer from kwashiorkor they are not confined to Africans Probably the changes in the texture are more fundamental than changes in colour. Mention may be made of Van Veen's curious observation (54) than in Indonesia, every now and then, the consumption of the wild tamarind (*Leucaenea glauca*) would cause a sudden total loss of hair, and, on regrowth, the hair is yellow-brown, soft and thin; this is sometimes seen in animals Further knowledge of this phenomenon might shed light on the precise causes of the hair changes of kwashiorkor, which may, in advanced cases, affect even the eyelashes and eyebrows which become dyspigmented as the disease progresses No work has yet been done to examine the relationship of these changes to the copper deficiency achromotrichia of Hundley (55, 56). The hair changes cannot be reversed by the administration of riboflavin or pantothenic acid but respond to proper feeding, normal hair growing out slowly.

The dermatoses—It is difficult in a review of this nature to describe the various dermatoses to which great attention, perhaps undue attention, has been paid Many, but not all, advanced cases show some dermatosis, and dermatosis is never present unless the case is advanced and never occurs as a single early sign as the dyspigmented hair may. Probably, typical, "crazy-pavement" dermatosis, as described by Williams (57) and Trowell (58), is peculiar to kwashiorkor. The more inert crackled skin seen best over the tibiae is not peculiar to kwashiorkor and is often seen in malnourished adults, but deep flexural fissures behind the ears and at the bend of the knee and elbow are possibly specific lesions (52). The pemphigoid type seen in Dakar is not peculiar to that region for it is also seen in Uganda and South Africa Secondary infection of the skin is common, while in some cases the lesions have approached an exfoliative dermatitis Attempts to ascribe the skin lesions to a single etiologic factor have all failed, and they are probably of a complex etiology and vary from area to area Among the factors that induce variation is the influence of the climate (6), and this is probably most marked in the regions bordering on, and affected by, the desert. In Kenya, Clark

The reviewer does not know of any detailed studies of the action of red pepper on the lower bowel but he feels that the conclusion of Brock & Autret

> It is reasonable to conclude that the practice of giving such enemas, which always achieve "results," leads to irritation of the mucosa of the large intestine

is a very conservative one, which is in the general tone of their excellent survey.

But, apart from such exotic practices, diarrhea is usually present. At first slimy green stools are seen; later, the diarrhea may be profuse and watery and the stools contain considerable quantities of undigested food. Steatorrhea is reported in many cases, but when the diet is very low in fat it is not readily apparent. When meat is given there is creatorrhea. In consequence of the usual composition of the diet undigested carbohydrate material is almost invariably seen. The diarrhea in the early stages is not accompanied by the passage of recognised pathogens, though at any stage an acute gastroenteritis may supervene, and in the later stages organisms of low pathogenicity may attack the devitalised gut. The diarrhea seems to be due to the inability of the gut to digest food. There may be excessive fermentation with gaseous distension of the gut, and this is probably a major factor in the production of the "potbelly" so widely seen in African children and so frequently photographed. Anorexia is a very variable feature. The appetite may be well preserved to the very end and much food taken, but on the other hand some children are irritated by an attempt at feeding and too apathetic to reach out for food themselves. A few cases exhibit positive anorexia and resist feeding. If there is no vomiting, and they can be nasally fed with skim milk, appetite recovers within a few days. Whether they have special preferences for food, especially for the proteins they lack, has not been studied.

The inability to digest the food given and the resultant diarrhea set up a vicious circle which, complicated by parasitism, is most difficult to treat, and is probably impossible of treatment under primitive conditions, and the child must be admitted to hospital. And even in hospital, attention is too often paid to the parasites and not to the underlying malnutrition. The failure of food digestion and the passage of undigested food in the stools again appear to be fundamental lesions in kwashiorkor.

Integumentary changes.—Integumentary changes are present in a variety of patterns, or may even be absent They show many puzzling features, extensively discussed by the Gillmans (6), and comprehended by Brock & Autret (1) in their term "dyspigmentation." This term, they suggest, should cover "reduction in the brown or black colour of the hair or skin of indigenous people as compared with the pigmentation as it previously existed in the individual concerned." It may not be merely a reduction in the quantity of the pigment but also a qualitative alteration. These changes are of importance in the history of the disease, but they are probably not fundamental lesions and undue attention to them, and to the dermatosis, has hampered progress in the study of the disease.

The Pathology of Kwashiorkor

Liver changes.—There is little doubt that in kwashiorkor there is considerable impairment of many organs and tissues of the body. Waterlow (62) has shown in children how malnutrition can lead to upset of enzymic activities in the liver, and there is reason to suspect that many enzyme systems throughout the body are upset, as might be expected in severe protein deficiency (63). Knowledge of the histopathology and functional pathology of kwashiorkor is at the moment fragmentary, but what is known so far fits into a coherent pattern. Many organs and tissues of the body require much further study.

The fact that fatty infiltration of the liver is very marked in the florid stages of kwashiorkor has been known for some years and has been studied in detail by the Gillmans and their associates in South Africa (6). The initial localisation of the fat is in the periphery of the liver lobule, often sparing the cells of the lamina limitans. As the disease progresses the fat appears nearer and nearer to the central vein till the whole lobule is full of fat (64, 65). With the increase in fat, there is an infiltration of the portal triads by round cells, and fine fibrosis appears round the periphery of the lobule, spreading out in a stellate fashion from the portal triads. The fibrosis results from a thickening of the reticulum around the peripheral cells. It spreads throughout the liver, until in severe cases a state resembling a Laennec's cirrhosis is seen. If the child survives, either with or without treatment, the fat tends to disappear slowly, first from the centrolobular region, and lastly from the periphery, leaving behind a fine stellate fibrosis and round cell infiltration in the portal triads. Treatment with protein leads to rapid fat reduction and a flooding of the sinusoids with lymphocytes (40), but does not affect the fibrosis and cell accumulations These may persist for many years, if not for life, and in an African appear to be a "hallmark" of kwashiorkor. Why they should be so persistent, when it is well known that in other conditions quite well-marked fibrosis of the liver can disappear, is a mystery, but it suggests that there is continuing liver damage of some sort The reduction of the fatty infiltration of the liver with increasing cirrhosis, a feature seen in the fatty livers of experimental animals (66), must be specially emphasised because the whole conception of fatty infiltration of the liver leading to cirrhosis in man has recently been attacked by Dible (67). His views must be regarded with great attention because of his many contributions to our knowledge of liver disease, but these views have been under attack (68), and his idea that there is no real differentiation between Laënnec's cirrhosis and multilobular hyperplasia is not in accord with the views of many pathologists who are satisfied that there is a distinction (69) Dible drew his conclusions from a study of a limited number of cases of human cirrhosis in West London and concluded that all his cases were the result of necrosis from infective hepatitis. It is by no means certain that infective hepatitis frequently leads to Laennec's cirrhosis (70), but Dible's statement, that the duration of fatty infiltration in humans is never long enough to be comparable with the periods of fat infiltration in experimental animals, is certainly unsound.

(53) noted that there were two peaks of kwashiorkor incidence annually, one characterised by edema, the other by dermatosis.

Mental changes.—Peevishness and mental apathy are very marked features of kwashiorkor, and in their psychological effects may be some of the most important components of the disease. In advanced cases, the child lies, a lump of silent misery, apathetic and indifferent till disturbed.

As Clark (53) says

the mental changes found in kwashiorkor are the most consistent and probably some of the most important of all changes found in the disease. They are I think far more characteristic, constant and important than the skin changes about which so much has been written. A child with kwashiorkor is dull, apathetic and miserable. It rarely cries or screams, a low miserable whimper is the only vocal sign of its wretchedness. We are all familiar with the African child who, terrified by the European doctor, fights and resists to the limit of its strength. Not so the kwashiorkor child. It will rarely if ever resist examination in the least degree and will never fight and scream—its apathy is too great. Children with kwashiorkor are so dull and apathetic that if put to sit in one place will remain sitting there till lifted up again. They never, as do so many other children, go wandering off down the ward to investigate matters for themselves If one can get a smile out of a child with kwashiorkor one can assume it is well on the way to being cured.

Less advanced cases are dominated by irritability; they cry on being examined or fed, or on interference.

On being cured, the children become bright, alert, and full of impish humour, but in this state they can rarely be kept in hospital and have to make room for others. The visitor, used to the rowdy cheerfulness of the children's wards of hospitals in temperate climates cannot help being struck by the quiet hush of misery that pervades the children's ward of an African hospital. This state of peevish mental apathy exists in many African children between the ages of nine months to four or five years. In nontropical medicine, this mental state is most nearly approached by children with severe pink disease. The possible significance of this mental state in children will be discussed later. Its exact etiology and pathogenesis are quite unexplored. The mental changes are unquestionably a part of the disease, do not show response to any specific therapy, and disappear *pari passu* with general clinical improvement. At present it would appear probable that they are directly related to the protein deficiency and the general enzymic upset consequent on this deficiency. If this is shown to be the case, it will open new fields of study and raise practical and theoretical questions of great importance.

Anaemia.—In the absence of parasitic infestation anaemia is moderate, but where there are many parasites, anaemia may be severe. The anaemia has recently been fully reviewed by Altmann & Murray, (59), Lehmann (60), and the Gillmans (6), and will not be discussed here Lehmann has claimed that reticulocytosis would completely explain the macrocytosis of the anaemia in Uganda, but this explanation is not acceptable to other investigators, and recent work suggests alternative explanations (61).

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In the tropics both the fatty livers of kwashiorkor and Laennec's cirrhosis are diseases of young children and of young adults, and are apparently in some close relationship. Dible is on more sound ground when he doubts whether the fat infiltration is the cause of the fibrosis. This doubt is general, for though the association is unquestioned, the mechanism is still in dispute. Fat may be present both in humans and in experimental animals for considerable periods without any evidence of fibrosis. In other cases, the fibrosis may arise early, as in kwashiorkor, and develop rapidly. On the other hand, the fibrosis will continue even when fat has disappeared from the liver, and the accentuation of the fibrosis as the fat disappears is an old observation. In kwashiorkor, there is a very close relationship between the fat and the fibrosis, but there is also evidence of a profound upset of liver function, such as may not be seen in fatty liver infiltration under other conditions (71). Many observers have noted that, in humans and in experimental animals, the liver may be grossly fatty without any marked abnormality in liver function tests, save perhaps of the sulfobromophthalein (Bromosulfalein) excretion (71, 72). In kwashiorkor, there is evidence of marked alteration of hepatic function as shown by the inability of the liver cells to synthesise glycogen from glucose (73), and by the Quick test, Takata-Ara test, thymol turbidity, and other tests (74, 75). Perhaps this is in part explicable by the fact that, where the fat has gone from the liver cells, they are not normal but show, in a marked degree, characteristics of the hypocytoplasmic liver cells of protein deficiency with much watery vacuolation (40).

Another feature of kwashiorkor suggestive of profound liver damage is the almost invariable rise in the γ-globulins. It has recently been shown by Popper and his associates (76) that these are manufactured in reticuloendothelial cells, particularly in the Kupfer cells and liver sinusoidal cells. In kwashiorkor, rise in the γ-globulins is marked, and is prolonged far beyond the clinical cure of the patient (46), and it seems possible that this rise is indicative of damage to the reticuloendothelial cells of the liver, continuing long after, and independently of, the fatty infiltration It is notable that the fibrosis of the liver in kwashiorkor is not due to fibroblastic proliferation but to thickening and collagenisation of reticulin fibers (64, 74). This is in agreement with the pathogenesis of Laënnec's cirrhosis as described by Moschowitz (77).

In adult Africans with kwashiorkor the same changes are seen as in children, namely, fat infiltration, fibrosis, and cell accumulations. There is one difference; the amount of fibrosis is greater in adults (64). This was thought to be due to the fact that the lesions occurred in a liver which had been previously affected in a childhood attack. It would appear unlikely that the occurrence of cirrhosis is due to a succession of episodes of acute fatty infiltration, although this is possible. Typical cases of kwashiorkor in older children and in the teen ages, though they do not show much evidence of fat in the liver, do show increased and progressive fibrosis. It would therefore

appear that the fatty infiltration is only a passing phase, and that, though fibrosis may start in association with fatty infiltration in kwashiorkor, there is separate damage to the liver leading to fibrosis It was in part this conception that led Trowell (78) to use the term "malignant malnutrition" for kwashiorkor. The term was intended to suggest irreparable sclerosis of organs, not the malignancy of a tumour, and in this sense has validity. The association of fatty liver infiltration with continuing damage to other organs is of great interest, since Hartroft (79) showed that in rats with severe fatty infiltration the fat-distended cells underwent a breakdown with coalescence into fatty cysts lined by a capsule of liver cells. Fibrosis developed near these cysts. While the fat is in these cysts it cannot easily be mobilised from the liver by the administration of lipotrophic factors. Such "lipodiastema," to use Hartroft's term, do occur in fatty livers of humans, but it is as yet uncertain if they occur to any extent in kwashiorkor. If they do exist, their evolution may play a part in the development of the fibrosis, and their breakdown may explain sclerotic changes in other organs. In further studies, Hartroft (80) has shown that the cysts may rupture into the bile ducts or into the lymphatics, in which they may do no harm, or they may rupture into the bloodstream and give rise to showers of fat emobli. Such repeated showers of fat emboli would explain some of the puzzling pathologic changes in other organs and might in part explain some of the neurological symptoms. Hartroft's brilliant work has opened interesting possibilities.

It also appears that fibrosis in the liver in African children may progress without fat ever having been present in the liver. Walters & Waterlow (81) in the Gambia have been studying liver biopsies in infants with edema, dyspigmentation, and enlarged livers which showed marked hepatic fibrosis from the age of a year onwards. The full report of these observations is not yet available but Brock & Autret (1), who have seen some of the cases, state that they differed clinically from typical kwashiorkor, only in that the disease often developed at an earlier stage (six to nine months) than kwashiorkor and while the children were still entirely breast fed. Platt (35) has suggested a further difference, namely, that the children were not given supplementary carbohydrate from an early age, but Brock & Autret (1) discount this A brief preliminary statement says that Russell (82) has examined the liver biopsies and believes "that they show a distinct continuing process, not due to malaria, or any infection, and with some resemblances to the condition found in de Toni-Fanconi disease." The fibrosis is apparently of a globose type in which portal triads become more and more bulky, although maintaining their shape and definition, and the stellate scarring seen in kwashiorkor is not apparent. In Uganda, such globose fibrosis is often seen with stellate scarring. The etiology of this globose fibrosis awaits explanation. It would not appear to be malarious, and as it occurs while the child is on the breast it is possibly due to a deficiency of the maternal milk. It appears to be a lesion distinct from those found in deficiency in lipotrophic factors.

In the tropics both the fatty livers of kwashiorkor and Laënnec's cirrhosis are diseases of young children and of young adults, and are apparently in some close relationship. Dible is on more sound ground when he doubts whether the fat infiltration is the cause of the fibrosis. This doubt is general, for though the association is unquestioned, the mechanism is still in dispute. Fat may be present both in humans and in experimental animals for considerable periods without any evidence of fibrosis. In other cases, the fibrosis may arise early, as in kwashiorkor, and develop rapidly. On the other hand, the fibrosis will continue even when fat has disappeared from the liver, and the accentuation of the fibrosis as the fat disappears is an old observation. In kwashiorkor, there is a very close relationship between the fat and the fibrosis, but there is also evidence of a profound upset of liver function, such as may not be seen in fatty liver infiltration under other conditions (71). Many observers have noted that, in humans and in experimental animals, the liver may be grossly fatty without any marked abnormality in liver function tests, save perhaps of the sulfobromophthalein (Bromosulfalein) excretion (71, 72). In kwashiorkor, there is evidence of marked alteration of hepatic function as shown by the inability of the liver cells to synthesise glycogen from glucose (73), and by the Quick test, Takata-Ara test, thymol turbidity, and other tests (74, 75). Perhaps this is in part explicable by the fact that, where the fat has gone from the liver cells, they are not normal but show, in a marked degree, characteristics of the hypocytoplasmic liver cells of protein deficiency with much watery vacuolation (40).

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conditions has been noted (87). But this is not the same as the cystic fibrosis of childhood (88). The changes in other organs that accompany cystic fibrosis of the pancreas are not seen in kwashiorkor. Although pulmonary infections are common, they are not associated with squamous metaplasia of the respiratory epithelium. Kristal (89) and other workers (90) have claimed to have produced cystic fibrosis of the pancreas by deficient diets, together with the appropriate changes in the lungs and other organs. But it is doubtful if this condition is a late result of a kwashiorkor-like atrophy because the changes in the pancreas are so dissimilar. No doubt in both diseases the same effects follow the absence of pancreatic secretion from the gut. The frequency of pancreatic sclerosis in Africans at necropsy has been noted in East Africa (64) It has long been known that in cases of Laënnec's cirrhosis in temperate regions there is very frequently a pancreatic sclerosis, an association which has excited much speculation. It may be that both lesions have a common etiology in nutritional deficiencies at some time in the life of the patient. But another explanation is possible, since it is claimed that in all cases of infectious hepatitis there is an associated pancreatic lesion (91). The diets given to tuberculous patients many years ago were of such a nature as to make it seem likely that nutritional deficiencies may have been responsible for the atrophic and fibrotic lesions in the pancreas associated with fatty liver infiltration, described by Saphir (92).

Renal lesions.—The renal lesions of kwashiorkor have been little studied but merit detailed examination (93). Attention has been drawn to the frequent finding of swelling or metaplasia of the capsular cells of Bowman's capsule, often with hyalinisation of the glomeruli, and pericapsular hyalinisation with fibrosis (64). The significance of these changes is uncertain. There is a constant slight albuminuria (75). It was no doubt the presence of the albuminuria that led the great pioneer of medicine in Central Africa, the late Sir Albert Cook (94), as long ago as 1903, to comment on the frequency of kidney diseases in African children ". . . the little patient being brought in a bloated condition, edema being everywhere present."

Other changes.—Dean (95) has found low figures for the blood urea, cholesterol, and serum amylase, all of which rise on feeding a high protein diet. The blood urea may attain remarkable heights before reverting to normal Among other changes, Dricot *et al.* (75) report a constant increase in the basal metabolic rate, of 30 to 40 per cent above the normals for young children of the same age, a substantial rise in the serum lipids without rise in cholesterol or phospholipids, and a slight decrease in the alkaline phosphatase of the serum.

Relationship of Kwashiorkor to Other Diseases

The heart in kwashiorkor and malnutritional heart disease—There is no doubt that the cardiovascular system is affected in kwashiorkor. Although cardiac lesions are not observed clinically in more than a very small percentage of cases, the circulation is impaired, coldness of the limbs is very marked,

The response of the fatty liver of kwashiorkor to administration of lipotrophic factors is disappointing and does not compare favourably with the response to high protein diets (83).

Pancreatic changes.—The influx and retreat of fat from the liver in kwashiorkor children, while there is continuing progression of the disease, suggested that there might be a more fundamental lesion, and it is now well established that before there are changes in the liver the pancreas is severely affected (40, 41, 64, 84,). The acinar enzyme secreting cells undergo a profound atrophy, while the ducts and the islets are unaffected. Similar changes affect the small intestine, the parotid gland, and possibly the lacrymal gland (40). The small intestine is thin, diaphanous, and markedly atrophic, all coats being affected, but in the initial stages the enzyme secretory cells are disproportionately damaged. There is a marked diminution in the secretion of hydrochloric acid, and probably of pepsin in the stomach (75). In the duodenum, enzymic activity is very low and may be practically absent (85). On protein feeding, the activity reverts to normal (85). The fact that atrophy of the pancreas precedes the fatty infiltration led to the suggestion that children with kwashiorkor had virtually undergone a pancreatectomy (sparing the islets), as a result of the malnutrition (64). Similar atrophic changes are seen in the parotid (40) which swells on protein feeding (42, 64), and it is surmised that similar swelling takes place in the atrophied pancreas, with resumption of function. This is shown by the disappearance of undigested food from the faeces The basic pathology of kwashiorkor would appear to be selective atrophy of those glands which lose enzymes by exocrine secretion, possibly because there is insufficient protein available for the manufacture of enzymes (40). This suggestion is probably too simple in itself to explain the pathogenesis of the disease. The reason why the pancreas and the small intestine are involved so severely is possibly that these children are not starved, but, while on a diet extremely poor in protein, are stuffed with carbohydrate, which leads to a continual demand for enzyme secretion. If protein can be made available, it would appear to be utilised in large part for the manufacture of enzymes which are then secreted and which can then digest the food given The rapidity of protein turnover in the pancreas and small intestine, greater than in other organs, has been established by Tarver & Schmidt (86).

In the later stages of kwashiorkor there is evidence of fibrosis of the pancreas, as there is of the liver. It is a periacinar, peritubular, and periductal fibrosis which leads to marked sclerosis (64). This has never, in the writer's experience, gone on to anything approaching cystic fibrosis of the pancreas (40). In the pancreas of cystic fibrosis there is no resemblance whatever to the pancreas of kwashiorkor. In the latter condition there is such a degree of atrophy of the pancreatic acini with so little activity of the acinar cells that a minimum of secretion is produced, certainly insufficient to block tubules and ducts. Occasionally in kwashiorkor children who die with vomiting and dehydration, the cystic tubular *degeneration recorded in uraemia and other*

tent of the blood and tissues is extremely low (52), and that the condition might be due to vitamin E deficiency is quite possible. It is interesting to note that of the lesions believed to be due to vitamin E deficiency in animals, some,—liver necrosis, muscular atrophy and testicular atrophy—all have counterparts frequently seen in Africa. Here liver necrosis is frequent, and there are present this heart disease involving myocardial changes, the so far [illegible]

endomyocardial necrosis. In this second condition, occurring in Bantu males and females, of any age, who were living on an extremely poor diet, chiefly maize porridge with white bread, tea and sugar, there developed signs of congestive failure with gross anasarca. The course was rapid with increase in venous pressure, great dyspnea, and cold limbs. The heart was much enlarged because of dilatation, and its beat was feeble. There was always diastolic gallop, and the blood pressure varied from 150 to 90 systolic and 90 to 70 diastolic. The usual types of cardiac disease could be excluded, and there was no response to thiamine. There was usually no evidence of parasites. Of 30 cases, 21 had signs of peripheral neuritis, seven had a pellagrous dermatosis, and one had enlarged parotids. Of 22 males, 16 had gynaecomastia and 14 had testicular atrophy. There was no evidence of renal disease. A continuation of the same diet that had been consumed outside hospital led to deterioration in the clinical state; "wholesome food" led to recovery in a few weeks but return to the usual diet precipitated another attack. When the condition was not reversible by the "wholesome diet" alone, no drug or known food factor caused any improvement. Testosterone had no effect. The mortality was high, 8 out of 30 dying, but in some of the others of severe degree of anasarca was surprisingly well tolerated.

Necropsy revealed the hearts to be enlarged and hypertrophied. There were none of the changes of "endomyocardial necrosis," no hydropic degeneration, no endocardial fibrosis. There was minimal interstitial fibrosis, but there was interfibrillary edema of the myocardium. All the fatal cases showed progressive liver disease of the kind seen in malnutrition in South Africa, i e , pigmentary cirrhosis This was also present in biopsy specimens. In 19 cases there was cytosiderosis, with portal fibrosis in 11 of these In three other cases fat infiltration was the only lesion, and in 11 this coexisted with the haemochromatosis Detailed studies of the histopathology of this disease have yet to be published, and investigations to establish the exact etiology are in progress It is, however, Gillanders' (101) opinion that malnutrition is the most important factor in this disease, and this is the opinion of those who have studied endomyocardial necrosis. If these opinions are upheld, there will be in Africa two "new" types of heart disease, both common, both quite distinct in their clinical and pathological features, and both caused by malnutrition. There are probably many other malnutritional syndromes in Africa, yet to be described.

and the patients feel the cold bitterly. The electrocardiographic changes were studied by Janssen & Le Roux (96). There was no bradycardia and the pulse rate did not change appreciably on recovery. All cases showed some abnormality in the major deflections, the most conspicuous being decreased amplitude in the QRS and T waves. The T waves were especially affected being of low amplitude, and isoelectric or biphasic. Vitamin therapy, including intramuscular thiamine, did not produce changes in the waves. On a good diet there were no changes for 7 to 14 days and restoration to normal took 21 to 30 days. It was concluded that these changes indicated myocardial damage. This is extremely probable for histologic examination reveals degenerative changes in the myocardial fibres, particularly in the subendocardial region, consisting of watery vacuolation and nuclear alterations (40).

These lesions are of particular interest because heart disease of apparently nutritional origin, and of at least two types, appears to be widespread in Africans. The first type was recognised by Bedford & Konstam (97) in African troops in Egypt during the late war. It particularly affected men from West Africa, and it is curious that it has not yet been recorded from that region. It is frequent in Uganda, where it was independently recognised by Davies (98, 99) and tentatively named "endomycardial necrosis." A watery vacuolation and degeneration of the myocardial fibres in the subendocardial region were the earliest lesions. They were often focal at first but later tended to become confluent and to affect wide areas. The fibres atrophied and died, but very slowly, there being minimal cellular infiltration though the vascular supply was normal. The dead fibres were slowly organised into plaques of white fibrous tissue which lay in the inner third or two-thirds of the myocardium and might contain walled-off areas of necrotic tissue. The endocardium was involved from an early stage and might be swept away by the necrotic process. Thrombus, often of considerable size, covered the endocardium and sometimes became infected so that many cases had been misdiagnosed as a mural bacterial endocarditis. The lesions were widespread throughout the subendocardial myocardium, affecting all chambers, but the more gross lesions were usually found at the apices of the two ventricles, particularly the left. The fibrous process often spread up the papillary muscles and the chordae tendinae and caused valvular incompetence by retraction from below.

Clinically, the patients, of either sex and of any age, but usually from 20 to 40 years old, appeared as cases of congestive cardiac failure, with very dilated hearts. They had a high diastolic pressure but very low pulse pressure. There was no response to any therapy. In the early stages there was often a blood and tissue eosinophilia of unexplained origin The condition was not associated with any other known form of cardiac disease. As yet the etiology is uncertain and so is its relationship to kwashiorkor. But it occurs particularly in malnourished people. It differs from similar cases reported elsewhere, and usually called atypical beri-beri, by the total absence of any hypertrophy of the heart (100). It is known that the vitamin E con-

of the pancreas, parotid, small intestine, and other enzyme secreting glands, with hypoproteinaemia and fatty liver infiltration. While various stages of this have been produced in animals, it is dubious how far the effects correspond to the lesions found in kwashiorkor. It is well known that the composition of the pancreatic juice can be modified by diet (110) and exaggerated changes and exhaustion of the gland might be produced by further modifications. Another possible line of approach may be by the use of antienzymes and enzyme inhibitors, for instance, the extended use of such compounds as the antitryptic substance in soya beans, which has recently been extensively studied. This substance, which is a protein of the globulin type, has been prepared in a crystalline state (111). It has been found to cause increase in the size and proteolytic activity of the pancreas in chicks (112). Its possible importance in the nutrition of children, who are known to develop proteolytic enzymes gradually in the first few years of life, has been stressed by Dean (113). There is also much scope for the classical type of nutritional experiments, such as those of McCarrison (114) and the Gillmans (6), on the administration of native diets to animals.

Relationship to other deficiency diseases.—Associated vitamin and mineral deficiencies very frequently accompany kwashiorkor, though they are not a fundamental part of the disease. Their correction may do little to assist cure, and may precipitate a crisis, unless the administration is exceedingly carefully controlled (45, 115) Of greater interest is the relationship of kwashiorkor to *mehlnährschaden*, a condition first described by Czerny & Keller (116) A possible identification was raised by both Waterlow (74) and by Altmann (117) and was discussed more recently by Brock & Autret (1) and by Stransky (15). The latter observer, in addition to studying kwashiorkor in the Philippines, had also observed *mehlnährschaden* in Vienna; so he is in a position to make an authoritative statement He points out how much these diseases have in common, both occurring in weanlings on diets low in protein but overabundant in carbohydrate, and manifested by edema, hypoproteinaemia, muscular wasting, and hepatomegaly owing to fatty liver infiltration Neither "crazy-pavement" dermatosis nor dyspigmentation are present in *mehlnährschaden*, although a reddish discolouration of the skin is recorded in some cases (118) It is possible, as has been indicated, to make too much of such skin changes.

The relationship of kwashiorkor to *mehlnährschaden* has been raised in an acute form by the work of Veghelyi (119), who, during the siege of Budapest by the Russians, seems to have displayed all the high qualities extolled by Meiklejohn & Passmore (5) in the face of imminent famine He made careful studies of a malnutritional disease of children who were largely cut off from the protein foods and were subsisting on a high carbohydrate diet, chiefly dried vegetables and fats. On this diet they developed hypoalbuminaemic edema, and diarrhea with the passage of undigested food in the stools The enzymic activity of the duodenal juice was lowered, there was atrophy of the pancreatic acinar cells and fatty infiltration of the liver with the distribution

Experimental production of kwashiorkor in animals.—Despite a vast amount of work on animals leading to the production of fatty livers, it is doubtful if anything approximating to kwashiorkor has yet been achieved. Friedmann & Friedmann (102) first recorded pancreatic acinar cell atrophy on low protein diets but did not deal with changes in other organs, and their findings have been duplicated by Rumyantseva (103), who also does not mention fatty liver infiltration. Veghelyi and his co-workers (90) claim, as does Kristal (89), to have produced, by the use of low protein diets, not only pancreatic atrophy and fatty liver infiltration but also changes resembling those of cystic fibrosis in the pancreas and elsewhere, changes which do not correspond to those seen in kwashiorkor. All the experimental work in which high fat diets have been used with relative or absolute lipotrophic factor deficiency may be dismissed as irrelevant, as such diets do not correspond with those eaten by kwashiorkor patients (104, 105). The early dietary experiments of the Gillmans (6) did produce kwashiorkor-like lesions but, in addition, a variety of changes not commonly seen in kwashiorkor and of which the pathogenesis is uncertain A diet to mimic that taken by kwashiorkor patients must be low in protein and fat, and very high in carbohydrate, and possibly in roughage.

Another type of approach has been made by Farber & Popper (106) and by Chaikoff and his co-workers (107) following the observation that ethionine, an antimetabolite of methionine, produces fatty liver infiltration, loss of body weight, diarrhea, and death. It has been shown that ethionine speedily produces loss of pancreatic acinar cell basophilia, acinar cell necrosis with edema of the interstitial tissues, and cellular infiltration, the ductal and islet cells being unaffected. The liver rapidly becomes fatty, the cells in the periphery of the lobule being first affected, with subsequent spread towards the central vein, but if the administration of ethionine is continued, the fat in the liver tends to decrease, while the pancreatic lesions progress. The lesions, as with pancreatic cell degranulation on a high fat-low protein diet, can be prevented by methionine. This work, admittedly in its early stages, would appear, at first sight, to mimic closely the lesions of kwashiorkor, but there are discrepancies The lesions could be produced in fasted females and in fasted castrate males, but not in intact males or females given testosterone, although this protection was short-lived In castrate males the continuous administration of testosterone led to prostatic enlargement, but the protective action against ethionine diminished (108). Ethionine, in the dosages used, produces necrosis of pancreatic cells, fat necrosis, and inflammatory infiltrates, lesions not seen in kwashiorkor. Smaller dosages and alterations in the diet might perhaps produce lesions more closely resembling those of kwashiorkor. The exact mechanism by which ethionine exerts its effects is not yet clear.

Deficiencies in other compounds, e g , other specific amino acids (109), may also lead to pancreatic atrophy and to fatty livers Essentially to duplicate the findings in kwashiorkor, the experimentalist must produce atrophy

notoriously bulky and characteristically contain undigested carbohydrate (78).

Trowell (122) refers to studies of African soldiers, who had been selected for military service as the fittest of their kind, and who, on testing, could only achieve levels of physical efficiency far below those of European troops. In an effort to bring these Africans up to comparable standards of efficiency, they were given excellent, carefully devised diets which were consumed in large amounts Certain malnutritional symptoms and signs did clear up, but European levels of physical efficiency were not attained, nor was the caloric consumption equated by weight gain or energy output. Examination revealed that considerable quantities of the food eaten were being passed undigested in the stool. The reasons for this were not elucidated at the time, and the problem is worthy of further study, but it is reasonable to assume that there was a failure of the digestive enzymes. These were definitely not cases of adult kwashiorkor, but it is not improbable that the supposed enzyme defects were a consequence of a childhood illness which left a persistent lesion, particularly of the pancreas. It is known that pancreatic fibrosis is common in the general African population, and changes in the parotid gland are very frequently seen (123) as in other tropical areas (124). Upon proper feeding of a kwashiorkor child, the parotid glands rapidly swell, and swollen parotids often occur in supposedly healthy African adults.

It is unlikely that damage sustained during childhood is confined to the glands secreting digestive enzymes. There is certainly persisting liver damage, it is probable that all organs are damaged to a greater or lesser extent, and the evidence is suggestive that the changes are irreparable. If this is true, it leads to a particularly somber conclusion, namely, that millions of Africans, and many other tropical peoples, are already so damaged that little improvement can be expected in their general condition as a result of an improvement of diet. We must direct attention as soon as possible to the protection of the children before another generation is nutritionally damaged It is no wonder that Brock & Autret recommended emergency action It remains to be seen if the speedy and efficient treatment of children with kwashiorkor will prevent the progressive lesions, or if there is a definite time limit before the damage becomes irreparable Moreover, the children in most danger are probably not those hospitalised but those who struggle through this phase unaided.

Protein deficiency.—This is not to say that general improvement in nutrition will not bring some good response. Most important would be an increase in the protein consumption in the tropics. The chief beneficiaries would be the pregnant and lactating mothers and the children It is the lack of protein which seems to influence the behaviour of so many diseases in the tropics. Those who teach in schools of tropical medicine often expatiate upon the fact that though they spend much time teaching about the tropical parasitic infestations, the diseases which the tropical practitioner will spend most of his time dealing with are not those due to parasites, but those which have

seen in kwashiorkor, and these changes disappeared with clinical improvement. Increase in the duodenal enzyme activity rapidly followed milk feeding. There was left a residual fibrosis of the liver. If the milk was stopped and the clinical condition again appeared, it was no longer reversible by further milk feeding. Now which disease was Veghelyi studying? The absence of integumentary changes would at first sight exclude kwashiorkor, but in all other respects the lesions, as Veghelyi recognised, are remarkably similar. If the diseases are identical, then a very interesting conclusion emerges. *The disease is no stranger to Europe and may have been common* in the past. This possibility has interest because of the suggestion made by MacPherson (120) that kwashiorkor, to the Akan tribes of West Africa, means "the child possessed by a devil," and he further suggests that it is the old syndrome of the "changeling" so familiar to the older Europe and enshrined in the folk lore of that continent. And to the observer familiar with these tales who watches the progress of a child from a healthy infant to a wizened, peevish invalid with lank, coarse hair, the comparison is intriguing. Kwashiorkor may also account for the references to pancreatic atrophy, and atrophy of the intestinal enzyme secreting cells, which crop up from time to time in the older pediatric literature dealing with atrophic infants (40). The inconstancy of these findings, which was so puzzling, was, no doubt, due to failures to distinguish between the various types of infantile atrophy.

Kwashiorkor and Malnutrition in Later Life

There are good reasons for suspecting that most African children pass through a kwashiorkor phase during the early years of life. The mortality is heavy, both from the disease itself and from the infestations and infections which accompany and interact with it. Many children survive but bear within their bodies the scars of the ordeal through which they have passed. As they grow to adult life they still consume a diet of the same type as that on which they developed kwashiorkor. The threat of a still poorer diet, owing to drought, crop failure, or pests, hangs over them constantly, and illness often lays an added burden which may precipitate another attack of kwashiorkor. There is no doubt that kwashiorkor, with a clinical picture and a pathology remarkably like that of childhood kwashiorkor, can occur in adults (64) and especially in lactating mothers (1). Such adult cases bear a close resemblance to those cases of nutritional diarrhea described by McKenzie (121). But Brock & Autret (1) recommended that the term kwashiorkor should not be applied in such adult cases. The writer sees no reason to accept this decision since clinically and pathologically the conditions are so similar in adults and in children. No doubt the liability to further attacks of kwashiorkor is at least partly due to the lesions of the childhood attack which have caused permanent structural and functional damage. In this respect, no doubt, the more important organs are again the pancreas and the small intestine, for there is suggestive evidence that defects of digestion and absorption of food are not uncommon in Africans. Their stools are

show evidence of renal damage, but the relief of the deficiency apparently leads to a reversion to normality. In adult life, a hypertensive state develops insidiously which, in its evolution, bears a closer resemblance to the essential hypertension of humans than does any other form of experimentally produced hypertension (135). The pathogenesis of this condition would appear to be, in part, elucidated, for it seems that there is failure of growth of the renal capsule in comparison to the growth of the whole kidney and thus compression leads to hypertension similar to that caused by a cellophane perinephritis (136). A low protein diet inhibits the development of the hypertension (133).

These very interesting experiments give substance to the idea, which has been long in the minds of physicians, that many of the diseases of later life, of uncertain etiology, may be due to a brief and long forgotten episode in childhood. It may be premature at the moment to try to relate the experiments of Hartroft & Best (132) to human medicine, but it is permissible to point out that similar relationships may perhaps obtain in human medicine A severe attack of whooping cough in a poorly nourished child might well precipitate a nutritional crisis which not only causes immediate damage to an organ but after a period of apparent reversion to normality may in later life lead to a progressive disease. Such relationships might well obtain in malnourished African children, but two factors might obscure their recognition, the shortness of life and the low protein diet. Essential hypertension, and especially malignant hypertension, are very uncommon diseases of Negroes in Africa (137) but are frequent in American Negroes Perhaps the low protein diets of Africa lead to conditions unfavourable to their development. The infrequency of atheromatosis and the exceeding rarity of coronary thrombosis in Africans may also be noted here (137), together with the possibility that these too are absent because of deficient diets. Those seeking to explain the etiology of many cosmopolitan diseases might well pay more attention to the behaviour of these diseases in the tropics.

Liver disease in Africans —One of the target organs in kwashiorkor is the liver, and though the damage to the liver may not be one of the most important lesions in the acute phase, there is suggestive evidence that it may be of overwhelming importance in the later stages and in the later life of recovered cases. The high incidence of damaged livers in Africans (138), and indeed in other tropical peoples, is notorious as is their liability to further liver damage following the administration of hepatotoxic drugs (139). The frequency of hepatic necrosis, of cirrhosis, and of primary carcinoma of the liver is well established (140). But recent work has indicated that there are other, more subtle ways in which malnutrition and liver disease may influence the pathology of tropical peoples, namely, by interfering with the normal metabolism of hormones so as to bring about states of hormonal imbalance A detailed consideration of the mechanisms involved would lead into the vast jungle of the hormones. Only a few important aspects can be mentioned. An interesting paper by Rinaldini (141) sets the background. He observes that the fact that

a world-wide distribution. Chief among these are infectious diseases. It is not clearly recognised how subtly different in behaviour are many of these cosmopolitan diseases in the tropics. Probably the background of malnutrition accounts for many of the differences, and the general deficiency of protein is a most potent factor (125). The work of Cannon (126) on the effects of protein deficient diets in altering the reactions of animals to infections has attracted much attention. However little relevance this work may have to infectious disease in the American people, no tropical physician can fail to be impressed with its relevance to his work, for Cannon's experimental findings in animals are commonplaces of disease in the tropics. The poverty of the leucocyte response, the tendency to leucopenia in infections, the weak and ill-sustained antibody response (127), the tendency of the infective process to spread, and the development of indolent lesions, are features only too frequently observed Nor does protein deficiency merely affect the response to bacterial infections; it applies also to parasitic infestations of all sorts. Thus Sadun *et al* (128) have shown in chickens how nematode infestations correlate experimentally with the nutritional adequacy of the diet, re-emphasising the recognised tendency of well-fed animals to free themselves of helminthic infestation (129). The observations point the way to an approach to the conquest of many types of tropical parasites which is more fundamental than the use of specific measures against specific parasites. It is legitimate to doubt whether mass treatment campaigns against specific parasites will lead to significant improvement in the health of tropical dwellers unless accompanied by the provision of a better diet. Tropical infestations are especially serious when they themselves deplete the body of protein, as in the case of hookworms.

The complexity of the relationships between nutrition and resistance to disease have recently been discussed by Schneider (130), who has indicated how some nutritional factors enhance and others depress resistance, and how the same factor under different circumstances may exert both actions. He considers that susceptibility and resistance should be considered as two entirely separate qualities. Despite the long recognised association between famine and epidemic disease, there has been no major epidemic in recent years which started in association with malnutrition (131), possibly because the development of an epidemic depends on changes in the virulence of the organism concerned rather than on nutritionally induced changes in the resistance of the hosts.

Hypertension in Africans.—Other cosmopolitan diseases are also likely to be altered in their occurrence in a community subject to widespread protein malnutrition, and amongst these is hypertension. The experiments reported by Hartroft & Best (132), and subsequently confirmed and amplified by Handler & Bernheim (133), and others (134), dealing with the occurrence of hypertension in adult rats subjected in childhood to a brief period of marked choline deficiency, are some of the most remarkable of recent years. The choline deficiency has to be pushed to the point where the young rats

estrogens, possibly produced by the adrenals, were important to ovariectomised rats He found that there could be marked inability to inactivate estrogens with no histologic alterations in the liver. The failure to inactivate estrogens occurred without fibrosis, necrosis, or haemorrhage, and when minimal fatty infiltration caused by alipotrophic diets was present. This tends to confirm the clinical impression that such endocrine abnormalities which have been noted are not necessarily accompanied by or due to severe degrees of liver damage, and are not necessarily seen where there is severe structural damage to the liver.

Hormonal imbalance in Africans.—Now there is mounting evidence that this work has extraordinary relevance to Africans and, indeed, to many tropical peoples (148). The frequency of structural and functional liver damage, the widespread consumption of diets deficient and ill balanced in proteins, in vitamins, and in other constituents, and particularly the frequency of fatty infiltration of the liver, are all well established features of African life It would therefore be expected that Africans would show many changes resulting from hormonal imbalance even in the absence of well-marked liver lesions

The histology of the anterior lobe of the pituitary in adult male Africans has been studied by Vint (149), who performed differential cell counts by Rasmussen's method. He found that the African male had 8 6 per cent more acidophils and 2 5 per cent less basophils than the white male. In severe liver damage, which Vint (150) had previously established as very common in Africans, he found an increased basophil count. He pointed out how in "normal" male Africans the cell counts corresponded closely to the figures given for white females by Rasmussen

Trowell (151) has produced figures of the extraordinary frequency of gynaecomastia in African males supposedly healthy and engaged in heavy work. The previously quoted work of Drumel (16) and Lambillon (17) on African females points in the same direction, namely, a general sex hormone imbalance, with a tendency to hyperestrogenism, reflected in both functional and structural alterations. It is not intended to imply that the mechanisms involved are simple They are obviously very complex, as the Gillmans (6) have shown in a lengthy discussion, and they lead to widespread alterations in many tissues and organs. Thus, there is the strange predominance of the parotid enlargement in males What part is played by the androgens in causing these changes is not clear. The capacity of the liver to deal with androgens is very great (152) and may be effective under conditions where the capacity to inactivate estrogens has been lost There is reason to suspect that these hormonal imbalances affect the build of Africans, their bone structure (153) and development, as indeed was long ago suggested by the physical anthropologists who did not realise the full implications.

Such sex hormone imbalance, combined with and in part owing to protein deficiency, must have far-reaching influences over the disease patterns of African peoples and may be manifest in remote fields. Thus, Clarke (154)

changes in organ weight resulting from prolonged malnutrition in some ways resemble those found after hypophysectomy, and can be in part reversed by injecting pituitary extracts, has resulted in the belief that the effects of malnutrition on organs are mediated by inhibition of pituitary secretion Indeed the process has been called "pseudo-hypophysectomy" (142). Rinaldini subjected young rats to prolonged inanition which caused a 30 per cent weight loss, and he then made detailed studies of organ weights in comparison to those of hypophysectomised rats. While he did find some evidence of pituitary hypofunction, this did not explain all the changes found. The adrenals and gonads were resistant to inanition but profoundly affected by hypophysectomy. He concluded that his experiments did not support the view that the primary effect of inanition is on the pituitary. He had previously shown that chronic inanition interrupted the estrus cycle in the albino rat and the ovaries underwent marked atrophy. Also he found that during inanition the pituitary anterior lobe accumulated gonadotrophic hormones, but that their release into the circulation was very restricted (143).

The altered hormonal balances associated with liver disease have long been recognised and their effects have been dignified with the title "Silvestrini-Corda syndrome." This whole subject was reviewed by Lloyd & Williams (144). The hormonal effects seen in liver disease—gynaecomastia, testicular atrophy, alterations in hair distribution, and other changes—imply feminisation and correspond broadly with the changes produced by administration of estrogens The explanation appears to lie in the inability of the liver to inactivate endogenous estrogens. Vanderlinde & Westerfeld (145) have recently studied the mechanisms involved in the inactivation of estrone in relationship to dietary effects in the liver. They confirmed that inanition increases pituitary gonadotrophins, while, as reported by Rinaldini, the uterus and ovaries atrophy; and they showed that the system for estrogen inactivation was separate from the xanthine oxidase system which, with many other liver enzyme systems (63) was also seriously depleted on a low protein diet. Mentz & Odendaal (146) studied the relationship between malnutrition and inactivation of sex hormones by the liver in relationship to sex physiology and growth in rats, using foodstuffs of great importance in African life. They concluded that B vitamins were essential for the inactivation of estrogens, perhaps being more important in this respect than the amino acids, lysine, and tryptophan. They decided that a certain balance between the B vitamins was essential, as well as a balance between the vitamins and protein, for the stimulation of growth increased the utilisation of vitamins necessary for estrogen inactivation.

The importance of protein and the delicacy of the balance is shown by the work of Ferret (147) who spayed rats, implanted estrogen pellets in the spleen, and, after an anestrus period, fed deficient diets. Diet poor in the sulphur amino acids and in tocopherol, and alipotrophic diets, speedily led to permanent estrus which could be equally speedily reversed by making good the deficiencies. He found some evidence to suggest that extra-ovarian

as frequently as in Europeans, if not more frequently (163) Most attention has been paid to primary carcinoma of the liver, the subject of a recent monograph by Berman (164). The great preponderance of this cancer in Africans and in other coloured people, in contrast to its infrequency in Europe and America, has been clearly demonstrated. In Africa, it is a disease of young adult males in the 20 to 40 age group, and a hepatocellular carcinoma is usually superimposed on a slowly progressive cirrhosis of the Laënnec type. There is a close connection with poverty and malnutrition. Animal experiments have so far thrown little light on specific etiological factors, chiefly because they have been concerned mostly with the use of hepatotoxic drugs (164) which lead to necrosis of the liver with post-necrotic scarring and not to the production of a Laënnec type cirrhosis. Furthermore the carcinogenic compounds used often produce a variety of tumours, benign and malignant, not only in the liver but in other organs as well (165). Such a multiplicity of tumours is not commonly seen in Africans (148). It is probably a mistake to consider the problems of primary carcinoma of the liver without reference to the general cancer picture in Africans, for there are striking differences from the European pattern.

It is of interest that all the organs primarily affected in kwashiorkor—liver, pancreas, small intestine, parotid glands—are all common sites of cancer formation in Africans (40). Further, tumours of the reticuloendothelial system, especially lymphosarcomata, are frequently seen, and there is a high proportion of malignant tumours of the male breast (148). Indeed, practically all tumours that can be induced in animals by estrogens (166) are common in Africans. Without venturing too far into the realms of speculation it is permissible to point out that malnutrition and hormonal inbalance appear to play a large part in determining the sites of occurrence and the types of cancer seen in Africans and in other tropical peoples.

CONCLUSIONS

This review is written to indicate the problems of the tropics and particularly of Africa in the hope that it may do a little to foster much closer collaboration between the experimentalists of the temperate world and the tropical world This can only result in benefit to the tropical peoples and may stimulate work that will benefit the people of the temperate regions. It is true that much is being done, but much more remains to be done. The rewards, in the health and happiness of future generations, will be great indeed.

has recently surveyed the incidence of skin diseases in Nigerian Africans, and compared with his figures those for skin diseases in Negroes in temperate climates, Indians in Calcutta, Europeans in Nigeria and in Europe, and white Americans. After exclusion of specifically tropical conditions, most of the observed differences could be explained on conventional grounds, but the remainder could only be explained on the supposition of hyperestrogenism in Africans. It is unlikely that the sex hormones are the only hormones whose balances are affected by malnutrition and liver disease. Liver disease is known to affect the thyroid and the adrenal glands and to interfere with the action of the antidiuretic hormone of the posterior pituitary gland (155). The work of Selye (156) on the effects of stress on the endocrine system has also to be considered; this has been briefly discussed by Trowell (157), in relation to the nutrition of the African, and by the Gillmans (6).

A full discussion of the possible effects of sex hormone imbalance in malnourished communities would unduly enlarge this review. It has interests far outside the strict field of medicine. It is too much to suppose that it is only a modern problem for the circumstances in which it arises must have occurred in the world before.

Psychological aspects.—It would seem very probable that such sex hormone imbalance exerts an influence over the mentality of Africans. The influence of malnutrition upon the psychology of the individual has been exhaustively discussed by Keys *et al.* (2). In Africa, weaning is usually delayed, with the result that the child becomes excessively dependent on the mother. The disease, in its most acute form, often follows the child's removal from the maternal breast and his displacement by his successor as the chief object of the mother's affection He may even be sent away to relatives and thus completely parted from his mother. The mental changes in kwashiorkor in childhood have been previously mentioned. A state of peevish apathy dominates the lives of many African children up to the age of five years—a period in which more favoured children are actively learning about the world around them, accommodating themselves to it, expanding and adjusting their personalities, and making their first social contacts. During this period, the African child is too often a whining, apathetic invalid, and this must be a great handicap to his development. All the psychological trauma to the child must be intensified if there is a prolonged period of invalidism, and, if this is survived, the child grows up under the shadow of hormonal imbalance.

All these factors must exert extremely important effects upon the African mentality, effects which are to date almost unexplored (158), but which offer an immense field for investigation. It is possible that the psychological factors are as important as the more obvious tropical parasites and climatic conditions in the explanation of tropical backwardness. The importance in

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DISEASES OF THE REPRODUCTIVE SYSTEM[1]

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Many significant contributions to our understanding of the diseases of the female reproductive organs have been made during the period which has elapsed since the previous review. It is regrettable that space limitations preclude mention of papers dealing with pregnancy

Anatomy, Physiology, and Chemistry

The pituitary follicle stimulating hormone (FSH) has been isolated by Li *et al.* (1) in electrophoretically pure form from the pituitaries of sheep. This protein, which has a molecular weight of 70000, causes only follicular development in the ovaries when tested in hypophysectomized rats.

The role of chorionic gonadotropin as a luteotropic agent in the human being has been clearly defined in a series of studies by Bradbury *et al.* (2). Administration of the hormone in a daily dosage of 5,000 I.U to 10,000 I.U. was found to induce a pseudopregnant condition, indicated by a prolongation of the functional life of the corpus luteum, the development of a decidua, and the prolonged excretion of pregnandiol. Chorionic hormone failed to influence the developing follicle, to revive a regressing corpus luteum, or to affect the secretory endometrium in a castrate. Since the action of this placental hormone was limited to the maintenance of a pre-existing corpus luteum, it appears to be the luteotropic agent that is responsible for the early development of the corpus luteum of pregnancy.

Anatomical evidence in favor of the view that the multiple loss of viability of the "second-rank" follicles associated with a single ovulation may play a useful role in the ovarian cycle is presented by Sturgis (3) The follicle of the monkey ovary which is destined to ovulate has a thin theca interna, whereas the follicles destined to undergo atresia have an hypertrophied theca interna Sturgis postulates that the transitory production of estrogen by the theca of the follicles in early atresia, taking place only during the few days between the stage of preovulatory swelling of the mature follicle and the established functioning of the corpus luteum, may provide protection against a sudden decrease in ovarian hormone which might otherwise result from follicular rupture and extrusion of the cumulus and liquor folliculi. This mechanism may sustain the pituitary-ovarian balance essential to the liberation of the most advanced egg and luteinization of the follicle from which it was released

In a continuation of their classic studies of early human embryos, Hertig & Rock (4) have obtained information which suggests that defective germ

[1] The survey of the literature pertaining to this review was concluded in July, 1951.

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dehydrogenase, is contained in a purified protein fraction of beef liver and in homogenates of rat liver, kidney, testis, and mammary tissue.

Employing an enzyme preparation containing phenolsulfatase, Cohen & Bates (10) have demonstrated that 5 to 89 per cent of the estriol fraction and 8 to 100 per cent of the estrone-estradiol fraction is conjugated as the sulfate in the urine of pregnant women. Although conjugation of estrogens with sulfuric as well as glucuronic acid had long been postulated, no sulfate-conjugated estrogen had previously been isolated from human urine, presumably because of the small quantity present.

Tissue localization and routes of excretion of a variety of estrogenic compounds have been investigated by means of radioactive methods. Hormonally inactive dibromoestrone labelled with radioactive Br^{82} was not found to undergo selective localization in the breast or uterus of 11 patients studied by Twombley and Schoenwaldt (11). Eight of the patients had a drainage tube present in the common bile duct, so that complete collections of bile as well as urine could be made. The biliary tract was found to be the principal route of excretion of dibromoestrone, 39 per cent of the radioactivity being demonstrable in the bile at the end of 24 hr. as against 18 per cent in the urine.

The physiologically active estrogenic compound diethylstilbestrol, labelled in the β-ethyl position with C^{14}, was found by the same authors (12) to exhibit no selective localization in the sex organs. The highest concentration in any solid organ was that in the liver. The principal route of excretion was the biliary tract, 70 to 85 per cent being eliminated in the feces while 15 to 30 per cent appeared in the urine. Less than 0 2 per cent of the C^{14} appeared as carbon dioxide in the expired air, suggesting that diethylstilbestrol is excreted from the body before it has been broken down into any simple substances such as acetate or ethyl alcohol.

The metabolism of a conjugated estrogen, estrone sulfate labeled with S^{35}, has been studied in rats by Davis *et al.* (13) and by Hanahan & Everett (14) No definite localization occurred in any of the target organs despite a marked estrogenic response. Various organ homogenates were examined by Hanahan & Everett (14) for an enzyme system capable of hydrolyzing the conjugated estrogen. Liver homogenate was the sole preparation found to be capable of effecting hydrolysis of this ester.

Hertz's important observations that folic acid is required for optimal tissue growth response to estrogen and that estrogen-induced growth in the genital tract can be quantitatively inhibited by the administration of folic acid antagonists have been confirmed and extended Brendler (15) has shown that the use of a folic acid antagonist partly, if not completely, interferes with the ordinary depressive influence of α-estradiol on the rat prostate. Inasmuch as no interference with androgen stimulation of tissue growth is occasioned by the folic acid antagonist, it appears that folic acid is not a prerequisite for hormonally induced growth in general but is only essential

plasm quality rather than defective environment is the main factor in the production of spontaneous abortion. Of 28 conceptuses found in women submitted to hysterectomy for various reasons, 12 were abnormal and 7 were certainly destined to abort. The defective ova showed multinucleated blastomeres, absence of the embryonic disc and/or the chorionic cavity, or profound hypoplasia of future placental tissue. The endometrium was normal in all instances.

The changes occurring in the connective tissue of the rat ovary during the estrus cycle have been the subject of an interesting study by Catchpole *et al.* (5). The ovarian ground substance was found to vary in a reversible manner from a rigid gel to a more fluid state. Alterations in the staining reactions of the ground substance indicate that the underlying process is a depolymerization of the polysaccharide components of the connective tissue. These changes are interpreted physiologically as responses to hormonal stimulation and functionally as a mechanism permitting parenchymal growth and structural rearrangements within the ovary.

The vascular pattern of the human ovary has been the subject of elaborate injection studies by Reynolds (6). The branches of the main ovarian artery show a helical spiraling with gradually diminishing diameters. Growth and development of this vascular pattern is seen in fetal ovaries from the seventh month of gestation until shortly after birth. Spiraling regresses after birth until at 4½ months of age virtually none is seen. The spiral arteries are most highly developed in sexually mature individuals, dwindling after the menopause until the main ovarian artery which traverses the hilus is the only remaining artery of consequence in the ovary. The timing of the growth and regression of these vessels suggests that the process reflects another of the trophic actions of the estrogenic hormone. For the author's interesting theories concerning the function of the spiral arteries and their role in the formation of ovarian cysts, his paper should be consulted.

Knowledge of the chemistry and intermediary metabolism of the estrogens is being extended both by classic methods and by radioactive tracer techniques.

The current practice of reporting the results of chemical and biological assays of estrogenic mixtures in terms of a single estrogen may soon be obviated by new procedures for separating and identifying the various estrogens by means of countercurrent distribution (7) and by paper chromatography (8). The earlier convention, necessitated by the technical difficulty of separating and identifying the estrogens, has long been recognized as undesirable because of the great differences in the biological activity of the various compounds. The new methods, which greatly reduce the difficulty, will permit differential determination of the estrogen content of biological specimens.

The existence of an enzyme system which catalyzes the conversion of α-estradiol to estrone *in vitro* has been demonstrated (9). The enzyme, a

The intermediary metabolism of progesterone has been the subject of a variety of studies. Employing bio-assay methods, Forbes (21) has determined the level of plasma "progesterone" during various phases of the human menstrual cycle, and Bryans (22) has made similar measurements during that of the monkey. Forbes found a progestationally active substance to be detectable in the plasma a day or two before, or concomitant with, a major rise in body temperature and before the occurrence of mittelschmerz. In most instances, progesterone did not disappear from the plasma until after the onset of the menses. The rise and fall of progesterone levels and the basal body temperature curve in a given cycle agreed rather closely. Bryans found that a progestationally active substance appeared in detectable amounts within the first week of the cycle and increased steadily in concentration. Ovulation was followed by a decline until the sixteenth or seventeenth day of the cycle, when the plasma level rapidly increased, the maximum concentration being attained near the middle of the luteal phase. During the latter half of the luteal phase, the amount of progesterone in the blood decreased, the vanishing point being reached by the time menstruation had begun These observations are in harmony with earlier evidence which suggests that the ovarian follicle attains some degree of competence to secrete progesterone prior to ovulation and frank luteinization.

Radioprogesterone administered to mice and rats was found by Riegel *et al.* (23) to undergo rapid metabolism and excretion, most of the radioactivity being found in the feces. The greatest accumulation of radioactivity occurred in the pituitary glands of both types of animals and in the adrenals of the mice.

Implication of the liver in the conversion of progesterone to pregnandiol is suggested by a study of Rogers & McLellan (24). Following the oral administration of progesterone to patients in whom T-tube drainage was instituted for the relief of common duct obstruction, small amounts of pregnandiol were isolated from the bile. The lack of progestational activity in the bile may mean that progesterone does not undergo an enterohepatic circulation as has been described for estrogens.

A number of observations concerning the physiology of endocrine glands other than the ovary are pertinent to the reproductive system. In a study of the persufflation curves of the fallopian tubes of myxedematous women, Mussio Fournier & Pan de Santiago (25) found the oscillations to be of smaller frequency and amplitude than those of normal subjects. Thyroid therapy restored tubal muscular function to normal, the change being coincident with clinical improvement and with an increased metabolic rate. This interesting result is not surprising in view of the beneficial effect of thyroid upon the sluggish myxedematous myocardium and gastrointestinal musculature.

Studies of the level of adrenal cortical function during the menstrual cycle and reproduction have been undertaken during the current upsurge of interest in adrenal physiology. The observation by MacKinnon (26) of the steady increase in the total white blood cell and neutrophil counts

for the proper utilization of estrogen, either in a stimulant or depressant capacity. That a purine antagonist is also capable of inhibiting estrogen-induced growth in the genital tract has been demonstrated by Hertz & Tullner (16). The inhibitory effect is reversible by adenine. It appears that folic acid and adenine, and their respective inhibitory analogues, can quantitatively determine the degree of response obtained in a tissue which is under maximum hormonal stimulation for growth.

Knowledge of the physiologic actions of the estrogenic hormone has also been extended by recent investigations. Much of the confusion which has surrounded the actions of estrogen and progesterone on the human uterus has been dissipated by an important study by Henry *et al.* (17). Tracings of uterine contractions were obtained by means of an intrauterine bag and cannula during normal cycles, in women with demonstrably abnormal corpora lutea and in women in whom artificial cycles had been induced with estrogen and progesterone. It was found that estrogen is not essential for the occurrence of uterine contractions, the human uterus being capable of spontaneous myogenic contractions during the greater part of its life. Estrogen does not increase uterine activity nor increase the sensitivity of the myometrium to pituitrin. Uterine activity is greatest during the years of sexual maturity and reaches a maximum of efficiency at the two times when it is physiologically called upon to expel its contents, namely, at the end of the normal cycle and the end of normal pregnancy. For the production of maximally efficient and typical luteal contractions such as occur at the end of a normal cycle, both estrogen and progesterone must act upon the myometrium for an adequate time and in suitable quantities and proportions. If either or both is deficient in amount, or the time of their action is too short, the contractions are less well developed than normal. Estrogen and progesterone are synergistic, not antagonistic, in their action on the myometrium.

The lower two-thirds of the female urethra has been shown by del Castillo *et al.* (18) to be a target of the estrogenic hormones. Similar in embryologic origin and histologic appearance to the vagina, the urethral epithelium varies cyclically in thickness with the level of circulating estrogen. This level can be inferred by cytologic study of desquamated urethral cells in the urine sediment.

Luminescent phenomena of the female external genitalia have been the subject of two interesting studies (19, 20). If the vulva is exposed to specially filtered ultraviolet light, a varicolored luminescence results. Prior to the age of seven, vulvar fluorescence is seldom observed, although it may be found transiently in female infants for a few days after birth. Approximately a year prior to the appearance of the secondary sex characteristics, the extent of vulvar fluorescence increases until finally the entire vulva fluoresces. A yellow color is characteristically seen in hypoestrogenic states and a purple color during active sexual life. Although the nature of the compounds responsible for the fluorescence has not yet been determined, it appears that the color changes are in some way correlated with sex hormone metabolism.

syndrome, and two had cortical fibrosis with luteinization of theca interna cells. These ovarian changes and the analysis of other endocrine stigmata are interpreted as suggesting that the anterior pituitary gland, adrenal cortex, and ovary participate in hormonal imbalances important in the genesis of endometrial carcinoma.

The third article (31) deals with the genesis of carcinoma *in situ*. Eleven of 64 patients with the disease had previous biopsies that indicated a background of endometrial polyps, cystic and adenomatous hyperplasia, and anaplasia.

Confirmation of the findings of Hertig and his collaborators is to be found in studies by Speert (32), Dockerty *et al.* (33), and Ingram & Novak (34) Speert's 14 patients of 40 or under with endometrial carcinoma were found to exhibit a high incidence of infertility, epidermidization of the cervical glands, hyperplasia of the endometrium, and cystic ovaries without recent ovulation. Of 36 patients in the same age group with endometrial carcinoma studied by Dockerty *et al.*, seven exhibited features of the Stein-Leventhal syndrome. Ingram & Novak have added four more to the 50 cases of carcinoma of the corpus associated with feminizing ovarian tumors. It is interesting that cervical and mammary carcinomas, while occasionally seen in combination with estrogen-producing tumors, are much less common than are associated cancers of the endometrium.

The possible role of cervicitis in the etiology of cervical carcinoma is discussed in an interesting paper by Gagnon (35), a consultant to many convents of the province of Quebec He has found the incidence of cervical carcinoma to be negligible in nuns, a group whom he regards as virtually free of cervicitis. In one group of religious there were no deaths from carcinoma of the cervix as against 12 from carcinoma of the corpus. Inasmuch as carcinoma of the cervix is eight times as frequent as carcinoma of the corpus in the general population, there should have been 96 cases of cervical carcinoma in this group of nuns.

The experimental production of leiomyomas in female rats is described by Pfeiffer (36). Animals in whom constant estrus was induced by testis grafts tended to develop leiomyomas if they lived long enough (death from pyometra was a frequent occurrence). An adenocarcinoma of the uterus, a tumor never previously observed in the colony, was found in a testis-grafted female who died at 816 days of age (37). Cystic hyperplasia of the endometrium and an endometrial polyp appear to have been produced experimentally in an aged female monkey given 120 mg. of estradiol benzoate by implantation plus 1,630 mg. of progesterone by mouth over a period of three years (38).

An interesting descriptive study of the *post partum* endometrial hyperplasia observed in diabetics treated with stilbestrol and progesterone is presented by Meissner & Sommers (39). The appearance of the endometrium of 50 consecutive diabetics who had *post partum* bleeding following the administration of progesterone and of large amounts of stilbestrol in peanut

during the follicular and luteal phases of the cycle, followed by an abrupt decrease during the bleeding phase, suggests that in man, as in the lower animals, there is a periodicity in adrenal function correlated with the sexual cycle. That adrenal function may be increased during the luteal, as compared with the follicular, phase of the cycle is suggested by the finding by Davis & Hulit (27) of a lower eosinophil count during the luteal phase. Pregnancy is apparently characterized by an increase in the level of adrenal cortical activity, the leukocyte count being increased and the eosinophil count decreased. Labor is associated with a progressive eosinopenia.

While adrenocorticotropic hormone (ACTH) and cortisone therapy have as yet found little application in gynecology, the administration of these hormones for other purposes has often been attended by amenorrhea as a side-effect. In view of the amenorrhea commonly accompanying Cushing's syndrome, this finding was not unanticipated. Sprague *et al.* (28) reported that four of ten women given cortisone or ACTH became amenorrheic during administration of the agent or for a prolonged period thereafter. Three of the four were young girls who had been menstruating three years or less, suggesting that their menstrual function was more easily disturbed than that of older women. The pathogenesis of the amenorrhea has not been elucidated.

Pathology

Circumstantial evidence favoring the view that excessive estrogen stimulation of the endometrium is correlated with successive morphologic changes culminating in endometrial carcinoma is presented in a series of papers by Hertig *et al.* The first of these (29) concerns a group of 32 patients in whom endometrial biopsies taken 1 to 23 years before the diagnosis of cancer were available for review. Those biopsies taken 15 or more years before the recognition of cancer were essentially negative, while most biopsies at shorter intervals were abnormal. Endometrial polyps and cystic hyperplasia were met most frequently 6 to 13 years before the diagnosis of cancer was made. Adenomatous hyperplasia and anaplasia were most common three to five years before cancer was recognized. Carcinoma *in situ* of the endometrium was observed six times, most often three to five years before the diagnosis of invasive carcinoma. Statistical analysis of the entire group of 500 endometrial carcinomas, from which the 32 cases were drawn, indicated a frequent association with obesity, diabetes mellitus, and nulliparity.

The second article (30) deals with a similar analysis of 30 reported cases of endometrial carcinoma occurring in adolescence and youth, and of 16 new cases, aged 19 to 35 years. Menorrhagia, sterility, amenorrhea, and obesity were frequently observed in these patients Their earlier endometrial biopsies showed polyps, cystic and adenomatous hyperplasia, anaplasia, or carcinoma *in situ* The ovaries were examined in 11 of the 16 patients. Three cases showed ovarian cortical stromal hyperplasia, four had cortical fibrosis with underlying follicular cysts as seen in the Stein-Leventhal

type is attributable, they believe, to metaplastic transformation such as occurs in endometriosis, or to a further differentiation of the Mullerian epithelium from the tubal to the endometrial type. The myosalpinx undergoes hypertrophic and hyperplastic changes as does the myometrium under similar conditions. Tubal inflammation is not a proven factor in the pathogenesis of the lesion but appears to be secondary or coincidental.

Histochemical observations designed to demonstrate the location of ketosteroids in granulosa-cell tumors, thecomas, and fibromas of the ovary are reported by McKay *et al.* (46). In general, the reactive materials were present *in the theca cells of thecomas and in the theca-like cells of the granulosa-cell tumors*. It seems likely that the thecal component of the granulosa-cell tumors, rather than the tumor cells themselves, is concerned in hormone production. Steroidal substances were not present in the collagenous connective tissue of thecomas or fibromas. It is concluded that histochemical studies are capable of differentiating active thecomas from hormonally-inactive thecomas and fibromas.

An important contribution to the classification of hormone-producing tumors of the ovary is that of Teilum (47). He has demonstrated that morphological congruence obtains between the ovarian tumors which have previously been described as "folliculome lipidique" or granulosa cell tumors of tubular or adenomatous type and the feminizing androblastoma (tubulare lipoides) of the testis. The ovarian tumors apparently originate from a testicular blastema in which differentiation in the direction of Sertoli and/or Leydig cells may take place. Dominance of Sertoli cells would account for the estrogenic effect of androblastoma tubulare lipoides of the ovary and testis; dominance of Leydig cells for the androgenic effect of arrhenoblastomas and of the so-called "adrenal-cell tumors" and "luteomas."

A follow-up study of 80 out of 122 known cases of arrhenoblastoma is presented by Javert & Finn (48). Of particular interest are the five cases of concomitant pregnancy and arrhenoblastoma which have been discovered. These resulted in the birth of one three-month abortus, two normal male fetuses, and two abnormal female fetuses. In one of the females, the urethra opened at the base of an enlarged clitoris and the perineum was intact from the urethra to the anus; in the other, there was marked enlargement of the clitoris without other genital anomalies.

The morphological identity of the ovarian hilus cells with the testicular Leydig cells is pointed out by Sternberg (49). The prominence of these cells at puberty, during pregnancy, and at the menopause, and their responsiveness to chorionic gonadotropin suggests that they may exhibit functional activity. Two cases of specific tumors of these cells and two cases of hyperplasia in all of whom there was masculinization are described. It appears possible that the ovarian hilus cells are a source of androgen in the normal female in addition to the adrenal cortex An additional case of virilism associated with a hilus cell tumor is described by Waugh *et al.* (50).

or cottonseed oil was remarkably uniform. There was a florid overgrowth of both glands and stroma unlike that seen in other hyperplastic states. It is thought that the picture was due to estrogenic stimulation unduly prolonged because of an inflammatory reaction produced by the oil and a slower rate of absorption owing to encapsulation. The lesion is not believed to be precancerous.

The endometrium associated with ectopic pregnancy has been studied in 115 cases by Romney *et al.* (40). Of these endometria, 39 per cent were secretory, 30 per cent proliferative, and 6 per cent menstrual. Dedidua was present in only 19 per cent of the cases.

Although the etiology of endometriosis remains controversial, new evidence has been adduced by exponents of both the implantation and coelomic metaplasia theories. An ingenious contribution to the pathogenesis of the disorder is that of TeLinde & Scott (41), who demonstrated that at least some part of the castoff endometrium is viable. Of 10 monkeys whose uteri were surgically inverted so that they were compelled to menstruate into the peritoneal cavity, five developed endometriosis. In addition, endometrium excised and autogenously transplanted throughout the pelvic organs, intestines, and abdominal wall of seven monkeys resulted in the occurrence of "takes" in six. The viability of castoff menstrual endometrium was demonstrated in another way by Keettel & Stein (42). These investigators succeeded in growing castoff endometrium obtained from menstrual fluid in tissue culture.

Endometriosis was seldom noted in Negro women undergoing laparotomy at the Harlem Hospital, the incidence of pelvic endometriosis being 0.1 per cent and of adenomyosis 1.14 per cent (43). The extent to which these figures reflect a racial characteristic, a cultural pattern tending toward early marriage and child-bearing, the frequency of endosalpingitis in Negro women, or some other factor, remains to be determined.

The coelomic metaplasia theory is supported by circumstantial evidence cited by Teilum & Madsen (44) Seven cases of endometriosis in which the lesion appeared to have been caused by hysterosalpingography are described The lesions displayed a topographically strict localization to the edges of the lipoid granulomata and the subgranulomatous interstitial spaces, resulting in some cases in epithelium-lined cysts, in others in the development of endometriosis. In one case it was possible three months after salpingography to demonstrate various morphological phases of development with transition of the surface epithelium of the ovary into metaplastic columnar epithelium of the endometrial type.

The pathogenesis of salpingitis isthmica nodosa is discussed by Benjamin & Beaver (45). They regard the lesion as acquired in a manner similar to uterine adenomyosis, the tubal epithelium penetrating the tubal musculature just as the endometrium penetrates the myometrium. The subsequent transformation of the penetrating glands from the tubal to the endometrial

phology toward undifferentiation are observed. Such studies promise a contribution to knowledge of cancer biology whose importance may transcend that already made on the diagnostic plane, and their outcome is awaited with the keenest interest.

The occasional usefulness of the vaginal smear in the diagnosis of nonuterine neoplasms is illustrated in a series of brief reports. Frech (57) describes a papillary adenocarcinoma of the ovary recognized by this method, while Finn & Javert (58) demonstrated tumor cells in the endocervical smear of a patient with primary carcinoma of the fallopian tube. Carter *et al* (59) describe their experience in 18 patients with carcinoma of the vulva studied by means of a genital smear. They have found the smear to be valuable in the differentiation of vulvar malignancy from lesions of venereal origin.

Staining techniques providing new cytologic and cytochemical criteria for the identification of cancer cells are being developed, and can be expected to contribute materially to the precision of cytologic diagnosis. An example of these techniques is the periodic-leucofuchsin reaction described by Fawcett & Vallee (60). This is based on two chemical reactions: (*a*) oxidation of the 1,2-glycol linkages of polysaccharides with periodic acid to produce aldehydes, and (*b*) staining of the aldehyde groups by the carbonyl or Schiff reagent, fuchsin-sulfurous acid. Both glycogen and mucopolysaccharides are stained a brilliant magenta by this method. Glycogen can be distinguished from mucopolysaccharides by immersing control smears in saliva or malt diastase prior to staining; glycogen is removed by such treatment while mucopolysaccharides persist. In a case of adenocarcinoma of the endometrium, red-staining extracellular material was observed in association with the groups of malignant cells but was not found inside the cells.

Attempts to employ the vaginal smear in the diagnosis of pregnancy and as a prognostic aid in threatened abortion continue, but must still be regarded as in a research stage In a series of 18 pregnant and 15 nonpregnant women, Foraker & Brawner (61) were able to distinguish between the two groups with an accuracy of 93 per cent by making differential counts of cervical smears stained for glycogen. A method for recognizing threatened abortion by vaginal smear changes is described by Benson & Traut (62).

Refinements in the technique of obtaining and preparing smears are described by a number of authors Kulcsar (63) has made a comparative study of 100 smears taken concurrently from the vaginal pool and from cervical surface scrapings in 24 patients with intraepithelial carcinoma. The smears from the cervical surface were found to contain larger numbers of malignant cells, rendering the diagnosis easier and more certain Neoplastic cells were found in 93 per cent of the cervical smears, as against only 55 per cent in smears from the vaginal pool. The magnitude of the differential between scrapings and smears varies considerably from laboratory to laboratory. Thus Graham (64) is successful in recognizing 90 per cent of cases of carcinoma *in situ* from a single vaginal smear

Diagnostic Methods

Progress in the interpretation of the vaginal smear is steadily enhancing the importance of this procedure in the diagnosis of uterine cancer. As pointed out by Papanicolaou (51), in the early days of the method the diagnostic objective was to decide whether malignancy was or was not present; the current objective is recognition of the type of the tumor, an advance made possible by increased knowledge of cell morphology.

That increased knowledge of cell morphology is improving the accuracy as well as the specificity of the diagnosis of malignancy is well illustrated in an analysis of "false positive" smears by Graham & McGraw (52). In 62 of 70 "false positive" smears in 7,544 negative cases, the positive report had been rendered on the basis of the presence of cells previously thought to be carcinoma but now recognizable as histiocytes, basal cells, or endocervical cells. The eight remaining cases still met current criteria for malignancy. Eight additional cases comprised a group in which the uteri of patients with positive vaginal smears unconfirmed by clinical and biopsy findings were the subject of special study. Four of these uteri proved to harbor a carcinoma *in situ;* the remaining four contained no lesion identifiable as carcinoma.

Cytologic criteria for the recognition of cervical carcinoma *in situ* have been perfected sufficiently to permit successful recognition of a high percentage of pre-invasive lesions. Achenbach *et al.* (53) recognized 82 per cent of 60 cases of carcinoma *in situ* and Nieburgs & Pund (54) suspected this diagnosis in 19 of 21 cases by examination of the vaginal smear. The cytological recognition of pre-invasive cancer is discussed by Reagan (55) in the light of his findings in 30 cases proven by histopathological examination. The cells, in general, are only slightly variable in size and lack the marked pleomorphism characteristic of cells from more differentiated squamous cell carcinomas Cells readily confused with those of carcinoma *in situ* include: (*a*) "atrophic" cells of the parabasal type from postmenopausal patients; (*b*) cells from benign cervical lesions characterized by acanthosis (condyloma acuminata, squamous cell papilloma, and leukoplakia); (*c*) cells from squamous cell metaplasia of the cervix; (*d*) cells from acute gonorrheal cervicitis.

From study of the morphology of the desquamated cells of preinvasive lesions, Graham (56) believes them divisible into two categories, one indistinguishable from invasive carcinoma and the other characterized by a [illegible] evidence [illegible] asmuch as serial cytologic studies of carcinoma *in situ* of this latter type may succeed in shedding light on the important question of reversibility, Graham urges: (*a*) that only patients whose smears contain undifferentiated malignant cells receive definitive therapy, and (*b*) that patients whose smears contain merely single well differentiated round cells be followed at frequent intervals, definitive therapy being undertaken only if changes in cell mor-

be ranked as among the most spectacular. Gonorrhea, lymphogranuloma venereum, and chancroid can now be classified as curable diseases and, thanks to the development of the newer antibiotics, granuloma inguinale appears to have become amenable to therapy as well.

The antibiotic spectrum of the gonococcus has been investigated by Gocke *et al.* (69). On a weight basis, penicillin was by far the most active of the agents tested; aureomycin and chloramphenicol ranked next and exhibited very similar activity; streptomycin and bacitracin were next, and were followed by neomycin and the polymixins. Sulfadiazine was the least active of the agents studied.

In a study of 35 patients regarded as harboring penicillin-resistant gonorrheal infections, 34 were finally cured with penicillin (70). No truly penicillin-resistant cases were found, the predominant causes of failure being reinfections and inadequate doses of penicillin. Successful treatment of gonorrhea with oral penicillin (71) and with streptomycin (72, 73) are also recorded.

Although the fact that the treatment of gonorrhea with penicillin entails the risk of masking concomitant syphilis is generally appreciated, Reekie (74) has made an important contribution to this subject. He reports the case histories of three gonorrheal patients, each of whom had a febrile reaction with chilly sensations and headache beginning from four to six hours after a single injection of 150,000 units of procaine penicillin. Each of these patients later developed syphilitic lesions in which the treponema pallidum was demonstrated. Inasmuch as the development of fever during penicillin therapy by patients with gonorrhea alone is extremely uncommon, an unexplained febrile or other reaction a few hours after the institution therapy should be regarded as a Jarisch-Herxheimer reaction until prolonged observation of the patient and repeated serological testing has proven otherwise.

Rapid healing of the genital lesions of granuloma inguinale is reported to result from the administration of streptomycin (75 to 78), aureomycin (79, 80), and chloramphenicol (81, 82). Evaluation of the relative merits of these agents awaits the accumulation of a larger series of cases and long-term follow-up

The diagnosis and treatment of genital tuberculosis has received close attention in recent years. The value of repeated cultures of the menstrual discharge of tuberculosis suspects is stressed by Halbrecht (83). Sixty cultures of the menstrual discharge of 16 women in whom biopsy had established the diagnosis of endometrial tuberculosis were made on the Petragnani medium; 12 of these cultures showed *Myocbacterium tuberculosis* A much smaller percentage of the cultures of intermenstrual cervical secretions were positive The possibility of repeating the studies as frequently as desired in order to establish the diagnosis enhances the value of the method in comparison with that of endometrial biopsy.

Although streptomycin is reported to have succeeded in eradicating a few cases of genital tuberculosis (84, 85, 86), this result has not been unifrom (87) However, streptomycin pretreatment of patients with genital tuberculosis about to undergo pelvic surgery appears to be of distinct value (88).

Another approach to the problem of concentrating malignant cells for microscopic examination is that described by Fawcett *et al.* (65). These investigators have succeeded in separating cell types in mixed populations by taking advantage of their specific densities. To do this a concentrated saline suspension of the fluid to be examined is layered onto an isosmotic solution of purified bovine albumin which has been adjusted by dilution to a specific density intermediate between the specific densities of the cell types that are to be separated. Then, after centrifugation, cells heavier than the albumin solution will pack at the bottom of the centrifuge tube while those that are lighter will collect at the saline-albumin interface. By the elimination of red blood cells, certain other cell types, and debris from vaginal fluid, the concentration and segregation of desquamated malignant cells is greatly facilitated.

The shortage of cytologists continues to limit the availability of the vaginal smear technique. Quick methods which utilize the histological knowledge of the conventionally trained pathologist are therefore being sought. An example of methods of this type is the "sponge biopsy" of the cervix. Sponges of gelfoam are rubbed against the cervix, fixed in formalin, embedded, sectioned, and subjected to microscopic examination. Although such preparations were found to exhibit less detail in nuclear structure than smear preparations, Rich *et al.* (66) are, on the whole, enthusiastic about their use. The sponge biopsy procedure did not equal the vaginal smear in accuracy but was superior from the point of view of time expended. The cell groups in question were either on the surface or embedded superficially in the gelfoam, obviating exploration of the entire slide. Reagan (67) succeeded in diagnosing 20 of 26 cases of proven cervical squamous carcinoma from examination of a single section of the gelatin sponge. Multiple sections of the six missed cases permitted recognition of three additional cases.

Pregnancy tests, both biological and chemical, continue to be given attention. Thorborg's (68) meticulous study comparing the sensitivity and accuracy of the Galli-Mainini and Friedman tests will be of value to all employing these methods. The frog test proved to be somewhat less sensitive than the rabbit test in the 1,042 patients examined. In 3 per cent of positive or weakly positive Friedman tests, the Galli-Mainini test was negative. However, the rabbit test gave one positive and two weakly positive tests which were false, whereas all three of these tests were negative by frog test. A positive Galli-Mainini reaction is therefore just as safe or safer than a positive Friedman reaction, while a negative Friedman reaction is more reliable than a negative Galli-Mainini reaction. The rabbit test appears to be preferable to the frog test when the rate of excretion of chorionic gonadotropin is moderate, i.e., very early in pregnancy, in ectopic pregnancy, and in the latter half of pregnancy.

Clinical Gynecology

Among the clinical advances during the period under review, the antibiotic victory over infectious diseases of the female reproductive tract must

phatic system and to reach the primary and secondary regional lymph nodes. When injected into the peritoneal cavity, the gold found its way into the retroperitoneal nodes, in which pronounced irradiation effects were noted.

The case for routine oophorectomy for women over 40 undergoing pelvic laparotomy is strengthened by a statistical analysis by Speert (101). Among 260 consecutive patients with primary ovarian cancer, 26 per cent had previous relevant operations. The patients were 40 years of age or older at the time of 52 per cent of the original operations, and 50 or older at the time of 20 per cent. The ovarian tumors were discovered within two years of 29 per cent of the original operations. The effectiveness of currently available estrogenic preparations is such that the rigors of the surgical menopause need no longer constitute a deterrent to prophylactic oöphorectomy, a practice for which Speert's data provide strong factual support.

A valuable analysis of the pathogenesis of stress incontinence is presented by Muellner (102). The mechanism of urinary control in the normal female consists of two components, the internal sphincter and the pubococcygeus portion of the levator ani. The pubococcygeus muscle is responsible for the descent of the internal sphincter at the start of micturition and it sharply elevates the bladder base to shut off the stream. Exertional incontinence results from failure of the pubococcygeus properly to support the bladder neck.

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Evidence suggesting that pleuropneumonia-like organisms may occasionally invade the female as well as the male genital tract is presented by Randall *et al* (89). "L" organisms were found to be present in the cervices of 78 out of 300 consecutive gynecological patients, being demonstrable with especial frequency in patients with leukorrhea. A case is reported of tubo-ovarian abscess from which a pure culture of "L" organisms was isolated. The clinical features of genital schistosomiasis (90), actinomycosis (91), and coccidiodomycosis (92) are presented in a series of papers of interest to all clinicians confronted with unusual lesions.

The treatment of carcinoma of the vulva is discussed in a valuable symposium (93). The current five-year cure rate of 12 per cent by radiological methods and of 22 to 25 per cent by surgical methods has been bettered at the Radiumhemmet, where a cure rate of 38 per cent has been achieved The 286 cases from whose response this figure was derived were treated with electrocautery of the vulvar tumor, combined with teleradium treatment of the glandular areas and with block dissection of the lymph nodes in cases amenable to surgical intervention.

Courageous attempts to achieve the total extirpation of cervical cancer are being made in a number of surgical clinics. An extraperitoneal pelvic lymphadenectomy operation whose aim is the eradication of regional metastases in the iliac, hypogastric, and obturator areas in postirradiated patients is described by Nathanson (94). Radical procedures for the removal of cervical cancers which have extended to the bladder and rectum are described by Brunschwig *et al.* (95, 96) and by Parsons *et al.* (97, 98). The operative mortality of these partial and complete pelvic exenterations has been high, and in survivors the management of the urologic complications of the procedures constitutes a formidable problem. The complications include: (*a*) oliguria secondary to shock or transfusion reactions, (*b*) fecal-urinary fistulas, and (*c*) hydronephrosis and pyelonephritis secondary to poorly functioning ureteroenteroanastomoses. Insufficient time has as yet elapsed to permit evaluation of these procedures in terms of the proportion of patients salvaged.

Radioactive cobalt and radioactive colloidal gold are being studied from the point of view of applicability to the treatment of cervical cancer. Forty patients have so far been given interstitial radiation with Co^{60} (99), advantage being taken of the soft beta and homogeneous gamma radiation emitted by this isotope. Radioactive gold suspended in pectin solution has been used as an interstitial therapy method for the treatment of transplanted squamous cell carcinoma in mice with excellent results (100). When injected into the paracervical tissue of normal rabbits, the gold was found to enter the lym-

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PSYCHIATRY[1]

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One cannot help but be perplexed by the current scope and volume of psychiatric literature. A recently compiled list (1) contains the names of 57 journals described as major English language periodicals in the field of psychiatry. Admittedly incomplete, this list includes the names of journals the contents of which are concerned with areas of scientific investigation and clinical application ranging broadly from morphology, physiology, and pathology of the nervous system to those concerned primarily with inquiries into the nature of social phenomena. Modern psychiatry, perhaps even more than medicine, has found itself in a pivotal position in what is being called "Human Biology." It continues to sustain its reciprocal relationship with the core of medicine, and subsequently with the physical and biological sciences basic to traditional medicine. It is being strengthened by its increasing use of the knowledge and skills communicated to it by psychology and the social sciences. Furthermore, it continues to accumulate knowledge and to refine its skills through its central position as a clinical or an applied science. Significant developments in specific fields may be summarized as follows.

Medical Education

In June, 1951, a national conference was held in Ithaca, New York, on the teaching of psychiatry in the undergraduate medical period (2). The conference was held under the joint auspices of the American Psychiatric Association and the Association of American Medical Colleges and was made possible by a grant from the National Institute of Mental Health. In addition to representatives of medical faculties and public health agencies, psychologists, social case workers, social scientists, and health administrators were invited to attend and to participate. The conference dealt with five areas, namely, (*a*) community needs, (*b*) the medical student, (*c*) the medical school as it exists today, (*d*) method and content of teaching psychiatry in the undergraduate medical period, and (*e*) administrative and organizational aspects of teaching in school and hospital.

A formal detailed report of the proceedings will be published in the near future. The plan of the conference made possible an intimate and vigorous exchange of ideas and experience among the participants. While many areas of critical importance to medical education were studied and reported, none, in the opinion of this reviewer, was more significant than the consideration of the changes in the concept of human biology. The statement which follows was submitted to the Conference by the Preparatory Commission assigned to study the "Medical School as It Exists Today."

[1] The survey of the literature pertaining to this review was concluded in September, 1951.

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team work between psychiatrists and social scientists He drew attention to recently published basic social science books and journals intent upon the development of logical, consistent, and systematic concepts that would serve as a basis for making predictions concerning the behavior of an individual in a given context of human relations. He remarked briefly on the symposium of the Milbank Fund (4), which was concerned with the epidemiology of psychoses and neuroses. The proceedings of this conference have been published in the past year. The papers of Knight, Leighton, Gordon, *et al.* on plans for study of the Epidemiology of Mental Disorder will interest a wide group of scientists.

Two papers read at the panel on The Study of Social Issues, American Psychoanalytic Association in Washington, D C., May 1948, were published during the past year. Parsons (5) stated that the basic frame of reference common to psychoanalytic theory and the type of sociological theory which is in process of development go back to the same basic conceptual scheme of the theory of social action. He concluded that psychoanalytic theory can make a crucially important contribution to the problems of the sociologist but that it is likely to be much more fruitful if it is adapted more specifically to sociological techniques and concepts. Hartmann (6) warned of the dangers of oversimplification in the application of psychoanalytic concepts to sociology and commented further on methodological difficulties encountered in current anthropological inquiries into the nature of "national character." From the psychoanalytical point of view Hartmann stated:

> the data actually used remain ambiguous so long as they cannot be analyzed with regard to motivational structure, dynamics, orientation to reality, to social reality itself, and to their history Obviously a concept of "national character," as of character in general, should include much more than statements concerning actual behavior, it should, we have a right to expect, tell us about the potentialities or behavior in relevant intrapsychic and other situations As previously stated, descriptive typologies do not sufficiently reveal such potentialities, for which we should need such dynamic and genetic typologies as are employed in analysis Though not genetic in

Although the two studies to be reported briefly exemplify the methodological and conceptual incompleteness discussed by Hartmann, they indicate the extension of clinical psychiatric interest in social phenomena. In the first, L Tyhurst (7) reports on the psychiatric study of displaced persons and immigrants in the area of Montreal in a paper entitled "Displacement and Migration: A Study in Social Psychiatry." Tyhurst differentiated between two distinct periods of the displaced person the first, lasting about two months after arrival, presented characteristics of a sense of well-being, a tendency toward increased psychomotor activity, a fostering of dependent attitudes toward the new environment, and a tendency to ventilate about war experiences, the second was a period of psychological arrival in which he noted an increasing appreciation of the current social situation together with a realistic awareness of language difficulties and differences in customs

Until recently man, sick and well, has been studied in terms of the physical and biologic sciences on the one hand and the humanities on the other. With the introduction of psychology and the social sciences in the collegiate pre-medical period and with the introduction of modern psychiatry in the undergraduate pre-clinical and clinical medical years, a change is taking place. As yet there has been no systematic [illegible]

the selection of what bodies of knowledge are to be communicated, when, where, how and by whom With the growth of the teaching programs of modern psychiatry in the medical schools and in the university teaching hospitals attempts are being made to modify the mind-body concepts of traditional medicine. A concept of personality has been introduced which offers an escape from the traditional mind-body or the mind-body-soul concepts. Through the emergence of dynamic psychiatry and through the contributions of projective psychology and anthropological studies further support was given to the hypothesis that man sees his surroundings according to his past experiences, particularly his early childhood experiences The interest in the mind-body dichotomy no longer plays a central part in medical philosophy. Instead, the interrelationship of man to his interpersonal environment has become the center of attention This may be summed up very briefly by stating that it is recognized that man does not develop into a person by an unfolding of his biological genetical endowment alone. He is born with the potential for development in an almost infinite number of patterns He only develops into a person by the assimilation of a cultural heritage which is transmitted extra-biologically through the culture's beliefs, ideas, prejudices, teachings, examples and so forth All individual attributes of personality have to do with the interaction between the given biological endowment with the persons who surround the individual, particularly those who surround him and raise him during early childhood. A major difficulty in medical education has been an attempt to teach an approach to man that considers that man can be understood exclusively through an unfolding of the genetic biological endowment in a given physical setting. It has, by and large, failed to integrate the interpersonal and cultural influences upon man's development, including his physiological equilibrium and bodily growth In so doing it has failed to understand the influences forming the individual person and the impact of the personality differences upon bodily functioning. The initiation of this approach has come into medicine through psychiatry. It entered into psychiatry through the recognition that emotional stress of man could be modified through alteration of the stresses of the environment on man or through alteration of the individual's attitude toward his environment. This had led to a closure of a circle in which it is now believed that man's modification of a person's environment or his attitude toward it can appreciably affect physiological functioning of the individual and of the homeostatic systems within the individual

The current operationally useful concepts of personality and culture, free from supernatural context, applied to medicine constitute in the reviewer's opinion an adequate answer to those who accuse medicine of having become too scientific. Obviously, medicine has not become scientific enough, it needs to apply scientific method to those areas formerly dealt with exclusively in religious and philosophic terms.

Social Psychiatry

Lindemann (3) in 1951 reviewed succinctly the evidence of increasing

Psychosomatic Medicine (9), with Spanish and Portuguese editions. The authors acknowledge the contributions of military medical experience in World War II to the increased acceptance of the psychosomatic concept in medicine. They have rewritten, rearranged, and added to the material of the first edition.

This reviewer read with interest and with sincere appreciation, John R. Reid's critical and penetrating comments on the definition of emotion in an introductory statement to Cobb's *Emotions and Clinical Medicine* (10). It is doubtful if Seguin's *Introduction to Psychosomatic Medicine* (11) will prove of practical value either to general practicing physicians or to psychiatrists. In the reviewer's opinion, the book is poorly organized, overambitious in scope, and limited in substantiation of the basic relationship between unconscious conflict and the somatization of anxiety.

Alexander's volume on *Psychosomatic Medicine* (12) can be recommended warmly to both general physicians and to psychiatrists. In the foreword the author states that this book, an outgrowth of an earlier publication, *The Medical Value of Psychoanalysis* has two objectives: it attempts to describe the basic concepts of psychosomatic medicine, and it presents existing knowledge concerning the influence of psychological factors upon the functions of the body and their disturbances. In its first part are included historical chapters on the roles of psychiatry and psychoanalysis in the development of medicine, together with methodological consideration concerning the psychosomatic approach. In its second part the author reports in substance long term systematic studies conducted by himself and his associates in the Chicago Institute for Psychoanalysis Attempts are made to indicate specificity of various patterns of behavior. Admittedly certain syndromes have been investigated psychologically more thoroughly than others A more detailed clinical psychological study of thyrotoxicosis is found in a later paper prepared by Ham, Alexander & Carmichael (13), in which they outline the specific dynamic pattern as follows:

> Frustration of dependent longings and persistent threats to security (exposure to death and other threatening experiences) in early life→unsuccessful premature attempt to identify with object of dependent cravings→continued effort toward premature self-sufficiency and to help others→failure of strivings for self-sufficiency and taking care of others→thyrotoxicosis This continued effort to mature, to grow up and be self sufficient, is the chronic emotional stimulus which via corticothalamic pituitary pathways activated the thyroid for long range effort and leads to clinical thyrotoxicosis.

Recent reports from the Cincinnati group of investigators on psycho-
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(14, 15, 16). A more general consideration of emotional aspects of cardiac disease is presented by Reiser in the *American Journal of Psychiatry* (17). His concluding emphasis on the significance of the doctor-patient relationship in the handling of the cardiac patient is of paramount therapeutic importance.

and values. With this, Tyhurst noted, there was apt to be a retrospective idealization with increasing concern with the distant past and childhood The author discussed further the more specific symptomatology of these persons and suggested that there may be constant factors in the psychopathology. The author believed that social mobility is the central social dynamic for the understanding of the various determining factors in the reactions of migrants. He distinguished between horizontal and vertical social movement, the former meaning movement of the individual from culture to culture, and the latter meaning movement from one social class to another. Tyhurst concluded that

> the psychological consequences of this process of change—in terms of increasing individualization, isolation, personal insecurity, the necessity for a reorientation of values together with an increased awareness of the relativity of previous stable values, all leading to failing communication, insecurity and anxiety—lie behind the psychodynamics of the migrant.

In a second paper, J. S. Tyhurst (8) reported on individual reactions to community disasters. The observations reported in this paper are based upon field surveys in four disasters: two large fires involving apartment house areas in towns of quite different social structure, a marine fire, and a flash flood He indicated that there is extensive psychiatric literature on individual behavior under stress and that this literature may be considered in the following frames of reference: (*a*) reactions, the psychological states associated with a stress situation; (*b*) factors, the various kinds of circumstance said to contribute to the reactions observed; (*c*) psychodynamics, character and mode of operation of the alleged relationships between the normal or abnormal reactions observed and the factors contributing to them. The author believes it necessary to add a fourth to the three frames of reference mentioned; namely, "the natural history" of the process during which these reactions are observed and during which the alleged factors are operating. A description of this natural history with respect to psychiatric phenomena in acute community disasters comprised the substance of his paper. In the pattern of individual reactions to an acute disaster, the author stated that at least three overlapping phases can be distinguished: (*a*) a period of impact, (*b*) a period of recoil, (*c*) a posttraumatic period. Each of the three periods may be characterized according to stress, time (duration and perspective), and psychological phenomena. The author proceeded to give specific data from his experience of each of the three periods in terms of stress, time, and psychologic phenomena He pointed out the usefulness of this approach in providing a more systematic study of processes and discusses its immediate predictive practical value in providing relief facilities. The author discussed further the relevance of the natural history method for psychiatric research in general. These studies will be of interest to many, including the practicing physician who is often called upon directly to meet the problems dealt with in these papers.

Psychosomatic Medicine

In the past year, Weiss & English have issued a second edition of their

ANESTHESIA[1]

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In revision of the literature on anesthesia, it is noteworthy how interwoven this specialty has become in recent years with other branches of the profession. Common frontiers exist with the different realms of the surgical specialties, of diagnosis, of therapy, and of obstetrics

With research workers of basic science, there is a common interest in the elucidation of our problems; in the rational use of drugs they have prepared and in the execution of methods elaborated by them. Indeed collaboration with these departments appears to be daily more frequent. Finally it is the common court of pathology which may divulge some of its secrets to aid the practice of anesthesia.

Before presenting this chapter, therefore, it has been necessary to probe into the work of all these groups in order to evaluate the year's progress.

BASIC CONCEPTS

Central Nervous System

By electroencephalographic studies in health and disease, during sleep, and in subjects under the influence of various drugs, various patterns have been obtained and classified These are suggestive if not always pathognomonic of underlying foci of abnormality and of the different stages of anesthesia Such studies are being utilized not only for the observation and controlled surgery of cerebral conditions but also for the investigation of cerebral influence upon the autonomic nervous system and in the accurate control of anesthetic levels (1 to 6).

The work of Quastel concerning the pyruvic acid oxidase system has progressed, and studies have been made with specific drugs At times it appears that a clear picture is not immediately available. Persky and his co-workers (7) have shown that this system is inhibited in the case of barbiturates at the dehydrogenase level, whereas Goldbaum & Hubbard (8) deduce from their work that depression of the carbohydrate metabolism is not the sole factor responsible for barbiturate narcosis. They found that picrotoxin had no effect on this mechanism although it is capable of waking an animal in the presence of anesthetic concentrations of barbiturates in the brain. They also found that picrotoxin had no effect on the distribution, degradation, and elimination of thiopental sodium (pentothal). Likewise, picrotoxin had no effect upon the glucose oxidation of normal mouse brain homogenate or upon the thiopental induced incubation of this metabolism. If the work and postulate of Foldes (9) proves to be correct in explaining the

[1] The survey of the literature pertaining to this review was concluded in September 1951.

MISCELLANEOUS

Both psychiatrists and physiologists will be benefited by study of Himwich's *Brain Metabolism and Cerebral Disorders* (18). We are indebted to him for a painstaking accumulation of data, heretofore unavailable in a single monograph. The material of the text falls into two divisions: the first, "Energetics," considers the methods by which energy is elaborated as well as distributed to support nervous activity; the second, "Patterns of Nervous Activity," explains energetics in terms of behavior.

The reviewer read with interest and profit Zubin's paper on "Objective Evaluation of Personality Tests" (19), in which he points out clearly the current limitations of such test procedures.

Volume V of Freud's *Collected Papers* was published during this year. In it one will find the important paper "Analysis Terminable and Interminable" and "Why War," Freud's reply in an interchange of open letters between Professor Einstein and Freud (20).

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factors which predispose to cardiac arrest in general cases as well as in intrathoracic surgery. An overdose of anesthetic drugs, coronary disease, myocardial insufficiency, hypoxia, this latter especially in the presence of the former two conditions, shock due to operation or to blood loss, vagovagal reflexes during surgery and at the time of intubation or extubation, and electrolytic imbalance may all be enumerated (21, 22).

Often difficulty is experienced in diagnosis either clinically or with electrocardiographic aid. Before evaluating this evidence and without wishing to appear retrogressive, the authors, who have both dealt with this condition conservatively and dramatically, can not help but reveal their thoughts by asking certain questions. How often has a patient with this condition recovered following conservative treatment? How many patients who have had a thoracotomy would have recovered without it? In how many has the thoracotomy per se proved too much for the patient? These questions can obviously not be answered with exactitude, but it is felt that they should govern the balancing of recent evidence presented

It would appear, therefore, (*a*) that all possible prophylactic measures should be taken to avoid the risk of cardiac arrest by noting the predisposing causes and (*b*) that if cardiac arrest can definitely be diagnosed, immediate effectual massage must be undertaken, and if the heart is in a state of ventricular fibrillation, it must be shocked out of that state. Emergency equipment should be available for this purpose. The technique is described in the references given

Other Cardiac Abnormalities

Burnstein and his associates (23) have continued their work concerning arrhythmias associated with intubation. A prophylactic intravenous dose of 1 gm DEAE (diethylaminoethanol) in 10 cc before intubation reduced the incidence of sinus tachycardia and ventricular premature beats from 68 per cent to 12 per cent. The opinion was expressed that topical anesthetization of the cords had no great effect in the reduction of this incidence.

General anesthetic drugs themselves, depending upon their concentration, may have either a stimulating or depressant action on the vagus mechanism. Johnstone (24) considers that inhibition is the result of a reflex caused by irritation of the nerve ends and strongly supports the administration of intravenous atropine to prevent ventricular tachycardia.

Studies have been made concerning the incidence of arrhythmias resulting from the use of ethyl chloride (25), vinyl ether (Vinethene) (26) and thiopental (27) These suggest that ethyl chloride is not contraindicated as an inducing agent for the following reason: vinyl ether is just as potent a cause of cardiac disturbances as any other agent in general use, and cardiac irregularities following thiopental anesthesia are due to hypercapnia.

The heart muscle itself, in dogs, has once again been shown to undergo changes directly due to the anesthetic (28) The insufficiency of the myocardium which occurs produces dilatation of the heart. Such a condition is

elevation of serum phosphorus levels, additional proof will be given to the enzyme theory of narcosis.

The effect of drugs upon the cerebral circulation may be of more than theoretical importance, as in the cases of coronary and renal blood flow. Schmidt (10) states that many drugs may give rise to cerebral vascular dilatation in the experimental animal, provided that the concentration is not sufficiently high to depress the vasomotor center and thereby cause a redistribution of blood The only exception to this rule, which is both common to man and animal, is the case of carbon dioxide, which stimulates the vasomotor center and dilates the intracranial blood vessels. Shenkin (11) is nearly in accord, but he shows that caffeine may actually reduce the cerebral blood flow in man. There appear to be no drugs which are uniform cerebral vasoconstrictors. The most evident occurrence of this is seen with a decrease in the carbon dioxide tension, in reality a release phenomenon (12). The sympathomimetic amines produce little or no effect. The reverse in fact occurs as a result of the general systemic effect of these drugs and is followed by a passive dilatation and increased blood flow. Schmidt (10) points out that the varying results in different species and the manner in which these results are obtained give rise to much discrepancy.

CARDIOVASCULAR SYSTEM

Cardiac arrest in animals.—Concerning cardiac arrest, a number of specific facts are relevant Ventricular tachycardia and fibrillation can be produced under a number of conditions.

The development of the cardiac sequelae can be guarded aganist by the prophylactic use of drugs e.g., quinidine (13) and Dibenamine (N,N-dibenzyl-β-chloroethylamine) (14), under conditions similar to those above It is more doubtful whether procaine or procaine amide always produces this result (15). It has been shown however that procaine is more effective in raising the threshold for cardiac stimulation and in prolonging the fiber conduction time than is quinidine (16).

That a heart in the state of ventricular fibrillation can be defibrillated by electric shock has been shown many times. Stearns and his associates (17) defibrillated a previously faradized heart with a counter shock of alternating current when cardiac massage and procaine were incapable of reversing the rhythm.

Cardiac arrest in man.—Cardiac arrest can occur either following ventricular fibrillation or in the absence of it (18); ventricular fibrillation can also occur following cardiac massage of a heart not previously fibrillating (19).

In the past, recoveries have been recorded in cases of clinical cardiac arrest treated by conservative measures Recovery is also reported following thoracotomy, cardiac massage, and electric shock therapy (19, 20) Deaths and irreversible cerebral damage are also recorded following this measure.

From the various work reviewed, it is evident that there are certain

differ in all three types. Whichever method is undertaken it is essential that there be an adequate tidal exchange of oxygen.

Sympathetic Blocking Agents

The sympathetic blocking agents have been compared and contrasted with each other and with the effect of nerve block (46). Their individual actions and therapeutic value concerning the circulation of the extremities have been investigated (47, 48). The care that should be taken in selecting an anesthetic for a patient who has already been subjected to sympathectomy has been pointed out by Felder and his associates (49), who found that gangrene developed on several occasions after the use of ether.

Myoneural Blocking Agents

The use of specific blocking agents in anesthesia is reminiscent of the names Claude Bernard, Laewens, and Griffith. The last named once stated that *d*-tubocurare would not be replaced until a drug superior in every quality was introduced. A number of drugs have been produced with this in view; meanwhile much has been done to elucidate the physiology of the myonerual junction. During this process, the drugs discovered which had the desired effect, except those related directly to curare, were found not to be physiologically comparable. There is every reason therefore that there should be different indications for their several uses

So much literature has been written on this subject that it is impossible to review it all. The authors have therefore decided to draft the following composite scheme [Some references are (50 to 61).]

Site of action—Depolarization of the muscle membrane at the motor end plate by acetylcholine is prevented by *d*-tubocurarine chloride (also dimethyl ether of *d*-tubocurarine iodide and chloride) Decamethionium chloride (C10, Syncurine) causes depolarization of the muscle membrane at the motor end plate in a manner comparable to unhydrolizable acetylcholine, without its muscarine effect.

Comparable doses—Doses comparable in effect are *d*-tubocurarine chloride 15 mg, dimethyl ether of *d*-tubocurarine iodide 6 to 7½ mg., Flaxedil [tri(diethylaminoethoxy)benzene triethyliodide] 100 to 120 mg, and decamethonium, the most potent but most variable, 3 to 4 mg.

Duration of action—The action of *d*-tubocurarine chloride lasts 30 to 45 min., that of dimethyl ether of *d*-tubocurarine iodide, 30 to 40 min., that of Flaxedil 25 to 30 min, and that of decamethonium 15 to 20 min.

Subsequent doses.—The curare preparations are cumulative, whereas decamethonium exhibits tachyphylaxis The action of ether enhances the effect of curare, while decamethonium opposes that of ether. Should decamethonium be preceded by curare, it is less effective.

Respiratory system.—Dimethyl ether of *d*-tubocurarine iodide is said to have the highest threshold on respiration; next in order of sparing is Flaxedil, then *d*-tubocurarine chloride, and finally decamethonium The first men-

seen, in decreasing order of severity, with chloroform, ether, divinyl ether, cyclopropane, and nitrous oxide. It has been demonstrated that when dogs are subjected to sublethal shock, a condition of fatty infiltration of the myocardium will develop (29).

Arterial Pressure

Many papers reviewed concern the importance of maintaining the arterial pressure in certain groups of patients (30). Davis and associates (31) report a group of 18 proven cases of coronary insufficiency or thrombosis; all were over 50 years of age, and all had experienced shock of over 1 hr. duration. Guyton and his co-workers (32, 33) have studied the ability of the body to maintain its arterial pressure under different circumstances. They emphasize the importance of the humoral mechanism following sudden loss or gain of blood and enumerate the different factors resisting arterial pressure changes. Fries and his associates (34), using the "Congestion-Collapse" technique with hexamethonium as blocking agent, demonstrate the importance of the role of compensatory vasoconstriction. Franklin (35) summarizes the circulation's economy as a whole and according to various systems in health and disease in two classical William Sharpey lectures.

The use of continuous vasopressors in conjunction with replacement of blood loss is emphasized by many. Deterling & Apgar (36) are impressed with the use of norepinephrine, especially in the instance of thoracolumbar sympathectomy, to achieve the maximum vascular, as opposed to cardiac, effect. The effect of norepinephrine on the coronary vessels, however, appears experimentally to be equivocal (37).

Thomas & Zuller (38) maintain that the aliphatic amines cause less stimulation to the central nervous system. The occurrence of the "after dilatation" effect with epinephrine is postulated by Swan (39) as being due to a central dilator effect of that drug. In spite of the care needed to maintain the arterial pressure in cases when this is essential, there are groups of patients in whom controlled hypotension may be employed.

The high spinal technique, used for many years as a method of minimizing blood loss. has been systematically employed by Gillies (40) in various types of cases, including sympathectomies Sympathetic block also has been found to be of use during the fenestration operation when additional advantage can be obtained by the compensatory vasoconstriction in the area of operation (41) Arterial exsanguination and infusion are being more widely advocated in selected cases, especially in vascular cerebral conditions requiring surgery (42, 43). The advent of pentamethionum and hexamethonium has provided yet another method of lowering the arterial pressure in a controlled manner (44). This method has been used during the operation of fenestration (45).

[illegible] is employed to render the area of operation as blood-

collateral respiration may give rise to postanesthetic complications and in what manner this mechanism may become depressed.

Many methods are being developed in order to make immediate observation concerning the concentration of gases and agents used during anesthesia and their solution in the human organism along with other important biochemical and physiological data. There is not sufficient space to describe them; it is however relevant to say that by the use of such methods, explanation is being given to various phenomena Careful study of these additional aids, when practical, can only result in safer anesthesia (71 to 75). An example is shown in the work of Molyneux & Pask (76) who calculated the liter flow of gases in a semiclosed system to prevent rebreathing of "utilized gases."

CLINICAL FACTORS

General Anesthesia

Premedication.—Stress is laid upon the individuality of premedication; this is reasonable, being in accordance with the widening margins of operative risk and age limits. The more classical drugs are still in frequent use, the dosage being modified for the particular patient Methomorphinan hydrobromide (Dromoran) was advocated because of the minimal respiratory depression, its adaptation to all ages, and its freedom from the accompanying complication of nausea and vomiting (77).

Inhalation anesthesia.—Gillespie points out that newer agents are by no means the safest, indeed several papers from both sides of the Atlantic have pleaded for simplicity (78) At the same time the general trend is to employ less toxic drugs or to reduce their concentration, adding when necessary specific items to fulfil the functions that one toxic agent produced by means of deep anesthesia. Thus intravenous supplementation to nitrous oxide and oxygen can, when properly controlled, yield all that the former agents did, with fewer pre- and postoperative complications. Combinations of nitrous oxide and oxygen with thiopental and/or meperidine hydrochloride (Demerol), by intermittent or continuous administration with one of the relaxing agents, have been reported on very favorably in all types of surgery. The analgesic, hypnotic, and/or relaxant may be added in the correct quantity if and when necessary in a complemental manner.

Comparisons of the analgesic agents used in this type of sequence have been made and analyzed by the multiple covariant principal (79, 80) From this work it appears that supplementation with morphine, meperidine, or morphinan was nearly comparable, the maintenance doses being 2 5 to 5 0 mg , 25 to 50 mg., and 1 5 to 3.0 mg., respectively. Meperidine produced the shortest period of postoperative analgesia and had to be given longer during the operation The incidence of hypotension was slightly higher with morphine.

A revival has taken place in the interest in chloroform. Waters (81) points out that the toxic action of chloroform still exists, but that the safety

tioned has several times been stated to have the widest margin of safety and to be that of choice for endoscopy.

Ganglionic effects.—Sympathetic and parasympathetic ganglia may be blocked by *d*-tubocurarine chloride, although this blocking is not usually of therapeutic value in doses given. Dimethyl ether of *d*-tubocurarine iodide does not have this effect. Flaxedil blocks parasympathetic ganglia and may cause tachycardia. Effects with decamethonium appear rare.

Synergistic effects.—Histamine release manifestations may be presented by d-tubocurarine chloride, and there may be an increase in heparin. Decamethonium and other synthetic preparations are less likely to produce these effects. It appears to have no synergistic effect with thiopental. Classical antidotes are of use with all but decamethonium.

Mephenesin (Myanesin) does not appear in this scheme as its position has been removed to that of treatment for spastic conditions and tetanus.

RESPIRATORY SYSTEM

The essential physiological factors calling for the absolute necessity of assisting respiration under some circumstances and the pros and cons of controlling it, with the subsequent physiological embarrassment, have been ably set down by Watrous and his colleagues (62, 63, 64). The methods by which these are achieved and possible sequelae if incorrectly performed are described in detail. Awareness of the possible deleterious effects upon the circulation is stated, and methods are advocated to minimize them.

It would appear that there is agreement concerning the effects upon the circulation of positive endopulmonary pressure or negative external pressure, as compared to electrophrenic respiration (65, 66, 67).

In the first instance, however, when this is undertaken as an anesthetic choice, there is a normal, or relatively so, cardiovascular system. By paying attention to detail such depression can be minimized, resulting in the advantageous use of this technique. With the latter two procedures and sometimes with the former, such are put into action by way of resuscitation. The patients involved would already show evidence of circulatory embarrassment which the positive and negative pressure can only exaggerate, while the electrophrenic type of respiration will be beneficial.

When the latter was pointed out, Sarnoff added proof that death in the case of a high spinal anesthetic is due to respiratory failure and not to cardiac arrest. The same holds true in curare poisoning; alternating positive or intermittent positive negative pressures will resuscitate a dog provided that heart failure due to anoxia has not already commenced (68).

Physiological respiratory assessment is being wisely applied to assay risk before surgery, especially of the thoracic type Such an assessment must be carefully studied and co-ordinated with clinical judgment. Comroe (69) has presented a method of estimating the degree of uneven alveolar ventilation which may be of use to the anesthetist and chest physician alike. Lindskog (70) has presented physiological reasons why the suppression of

Paton (94), who describe experimentally a release of histamine from the skin and muscle, following its use. Rubin & Winston (95) have studied the incidence of nausea and vomiting from the standpoint that it may be caused by the sensitization of the vestibular apparatus, or alternatively by direct stimulation of the vomiting center or by cerebral anemia. From other work it is deduced that the prophylactic use of dimenhydrinate (Dramamine) is beneficial (as it also is following the fenestration operation), whereas amphetamine and pyridoxine are without benefit (96, 97, 98).

Spinal and epidural anesthesia.—Since the world wide publicity which was given the incidence of complications following spinal anesthesia, the eyes of the medical profession have been focused upon this factor (99). This has proved excellent in many ways, as it has prompted analysis of the situation. Several large series of spinal anesthetic cases have been reported describing the various techniques and complications In spite of the crippling conditions which are inevitably seen at the big neurological centers, the general impression remains that such conditions are in reality rare and that there is no need to abandon a sound form of anesthesia when indications arise for its use.

Steps have been taken more generally to modify techniques in order to *minimize all types of complication resulting from spinal anesthesia. The etio*logical factors concerned in the production of spinal headaches, which have been discussed for a lengthy period, have met with more universal agreement (100, 101). The wider usage of small gauge lumbar puncture needles to reduce the incidence of headache is producing gratifying results (102, 103). The relationship between the altered cerebrospinal fluid dynamics occurring in abducens palsy and that causing headaches has been emphasized (104, 105)

The higher cell count in the cerebrospinal fluid which is found following continuous spinal anesthesia with the catheter technique may be a factor in producing a larger number of headaches than are seen following the single dose method (106). Polyethylene tubing may prove to be less irritating to the meninges than is the gum elastic catheter, and being used as it is in conjunction with a smaller (gauge 18) directional needle, it may replace the catheter The incidence of headache following the employment of such needles has been reported to be as low as 4 4 per cent (107). The relative values of polyethylene and Vinylite plastic tubes for use in the subarachnoid and epidural spaces has been the subject of investigation in a large number *of cases by Davison, Hingson & Hellman (108).*

There is one other complication of spinal anesthesia which the authors feel is worthy of comment This complication in no way affects morbidity, but it leaves to speculation a number of fascinating possibilities concerning the pathogenesis of phantom limb pain. Allusion is made to the cases reported by Harrison (109) of accentuation of phantom limb pain following induction of spinal anesthesia, in one case as high as T 5, for operations subsequent to the original amputation.

Further work has been done on the prolongation of anesthesia produced

factors lie with the knowledge of the administrator of the indications for its use and in the details of the technique of administration. The rate of increase in the concentration of chloroform during induction, the avoidance of anoxia, and the depth of the maintenance are important factors in obviating the complications. Reassessment of the actual concentration of the drug in man during third stage anesthesia has been made and appears to be about half the former concept (81, 82, 83).

Intravenous anesthesia.—A revival has been made with the use of intravenous secobarbital sodium (Seconal Sodium) in a new solvent, 50 per cent polyethylene glycol. The indications for use are similar to those for other short acting barbiturates. With this drug, respiratory depression of a mild order was observed in 70 per cent of patients and circulatory depression, also minor and transient, in 60 per cent. Laryngospasm occurred in 1.2 per cent of cases (84).

In the field of the ultra short acting barbiturates, Kemithal (the sodium salt of 5-Δ^2-cyclohexenyl-5-allyl-2-thiobarbituric acid) and thiamylal sodium (Surital) are still competing with thiopental. There would appear to be no immediate indication that thiopental will be superseded, although the majority of articles concerned do state that thiamylal sodium produces less respiratory and circulatory depression and that with its use the incidence of laryngospasm is low (85, 86)

Intubation—An easy method of intubation under thiopental, without aid of a relaxing agent, is advocated by Hunter (87) who makes use of the fact that following a sleeping dose of thiopental, the cords can be topically anesthetized by spray, without danger of laryngospasm. The subsequent major dose of thiopental, given after a pause during which the patient is oxygenated, produces adequate relaxation for laryngoscopy and intubation.

Ruben & Andreassen (88) have observed that the laryngeal reflex following meperidine and a relaxing agent is obtunded, and they report no stridor or laryngeal spasm when using this method for intubation and endoscopy, though respiration may be depressed. In cases of laryngeal spasm, Sadove & Balagot advocate the use of 35 mg Trasentin (diphenylacetyldiethylaminoethanol) intravenously which they state releases the spasm within 30 sec. in the majority of cases, giving long enough time in which to intubate (89).

The sequela of laryngeal granuloma has been investigated by different groups during the past year; it is evident that it occurs more frequently under certain conditions. A summary of these conditions reveals that the effects of trauma, blind intubation, an oversized tube, constitutional factors, nasal infection, a pharyngeal pack, the possibility that some lubricants may produce a contact dermatitis, and friction of the tube may cause this rare but annoying complication (90 to 93) The fact that the granuloma occurs in the area of the arytenoid processes suggests an indication for the use of a double curved tube which has been reported before (90).

Postanesthetic nausea and vomiting—The role that morphine plays in the production of so-called idiosyncracy has been investigated by Feldberg &

to the contrary (128, 129). Prolonged blocking of somatic and sympathetic nerves by a serial method via a plastic catheter has met with success (130, 131).

The necessity for the anesthetist to be familiar with every type of nerve block has become more apparent, there being very definite indications for their use. This fact is well appreciated after study is given to papers emanating from various schools. There has not come to the notice of the authors the description of any new techniques in the anesthetic application of nerve block, but there have been different assays concerning the drugs used. In this instance, the advantages of long acting drugs at ranges of low toxicity, for example, 0.15 per cent tetracaine and 2 per cent lidocaine, have been extolled (132 to 137). Concerning the toxicity of lidocaine, the consensus of opinion is that it is less toxic than procaine, although there is no absolute uniformity in this matter.

In this search for local agents with long action and low toxicity, metahydroxyprocaine has been given trial and has been found to possess more potent action and to be less toxic than procaine (138). The interesting relationship between the antihistaminic and local anesthetic drugs has been further studied (139). The use of hyaluronidase does not appear to increase the incidence of successful nerve blocks, with the possible exception in the case of the pudendal block (140, 141, 142).

Intravenous procaine therapy still remains an important therapeutic aid, but by trial and error it is finding its own level. Interested readers are referred to the monograph on the subject by Graubard & Peterson, edited by Adriani (143). Experiences with intravenous tetracaine have also been described (144).

Anesthesia in Special Types of Cases

The poor risk patient.—Many articles have been reviewed by the authors concerning patients in this category. Although nothing particularly new lies in the material employed, there is unanimous expression given to the factor of individual treatment before, during, and after operation. This applies to drugs used, techniques employed, postures adopted, electrolyte balance, and the like; emphasis is laid upon the effects of all these on a patient who has already suffered physiological trauma (145 to 148).

Thoracic surgery.—A number of observations carried out with the chest open reflect upon the circulatory system, the respiratory system, and the blood chemistry (149, 150, 151). There is still no unanimity in the type of anesthesia employed for major chest surgery, but each type appears to be selected with the foregoing factors in mind. Surgery is only undertaken after thorough preoperative respiratory studies; and it is followed by diligent postoperative care (152, 153)

Pediatric anesthesia.—Leigh & Belton (154) have stressed the anatomical, physiological, and biochemical differences obtaining between the young and the adult. They quote from Smith, whose book, *Physiology of the New Born*

by spinal agents with the addition of vasoconstrictors. The present situation suggests that norepinephrine (Levophed) increases the action of the drug as much as 75 to 100 per cent (110), while epinephrine and phenylephrine hydrochloride (Neo-Synephrine) augment it 50 per cent; ephedrine appears to be much less effective (111). There is no evidence to show there might be an increase in the number of complications. The possible systemic effect of intrathecal epinephrine, which might preclude the use of cyclopropane as an adjunct, has been experimentally discounted by Howard, Levi & Adriani (112).

Tuohy and his associates (113) assessed the spinal anesthetic effect of barbiturates. Anesthesia was uncertain, more complications occurred than usual, and sometimes a pronounced soporific effect occurred. Differential spinal anesthesia is still being found useful in diagnosis, though not as markedly as was earlier anticipated Analogous to differential spinal anesthesia is the selective blocking of sympathetic nerves in the epidural space with a dilute solution of a local agent, 0.1 per cent procaine continuously, 30 cc. 0.5 per cent procaine, or 30 cc. 0.02 per cent tetracaine (Pontocaine) (114). This method has been used to obtain sympathetic paralysis for bloodless field surgery. Such an approach has also been utilized for the successful treatment of thrombophlebitis (115). The efficiency of extradural block is said to be increased by the use of lidocaine (Xylocaine) (116, 117). Conner & Dripps (118), using a "local" spinal anesthetic of the piperidine group, viz., β-(2-piperidyl)-ethyl-o-aminobenzoate hydrochloride (Lucaine), have demonstrated the possibility that sensory anesthesia can be obtained without motor anesthesia, which might be advantageous in fluoroscopic work and in certain types of obstetrical cases.

Although the hypotensive states have been mentioned earlier in this chapter, it does not seem redundant to state here that Neo-Synephrine, [Methoxamine] β-(2-5-dimethoxyphenyl)-β-hydroxyisopropylamine HCL, and *d*-desoxyephedrine have been considered the most effective vasoconstrictor drugs for the maintenance of arterial pressure during spinal anesthesia (119, 120, 121).

Regional Anesthesia, Diagnostic and Therapeutic Nerve Blocks

Papers concerning the physiopathology of the mechanism of pain, which are well to study in conjunction with the clinical application of nerve blocks, have been reviewed in order to interpret the results of work in this field (122, 123). Since the impetus given by the past war to this procedure, many reports have revealed a large series of results, some during the current year of review (124, 125, 126). Some of the earlier reports of success appear to have been modified; and indications for this therapy have assumed more modest proportions.

The incidence of complications directly referable to this procedure have not been overlooked; these complications are of special significance in the neck and thoracic regions (127). The benefits derived from stellate blocks in cases of cerebral vascular accidents are far from convincing in spite of reports

series following this regime, there was no morbidity to either mother or fetus; whereas following the deep anesthesia technique, stillbirths, neonatal deaths, and vaginal bleeding occurred (171).

This section can not be closed without further reference to the interest shown, in many quarters, in the specific aim of lowering the neonatal morbidity and mortality rate by thoughtful obstetrical anesthesia and physiological methods of resuscitation Papers such as that by McKain, Belnap & Beck (172) go a long way to stimulate the efforts of obstetrician and anesthetist alike in this respect.

Postoperative Care and Resuscitation

Without going into detail, as the number of articles reviewed on these subjects has been great, it is certain that far more attention is being paid to the postoperative care of patients. To this fact, the increase in the number of postoperative recovery rooms in operation bears witness. Lowenthal & Russell (173) describe such facilities as being life saving and economical.

Here arises discussion on blood transfusion and oxygen therapy. Little new on these subjects has been reviewed by the authors, except that it appears that more care is being used in administering blood both in the elimination of reactions and in the control of the amount given (174) Rapid blood transfusion by the intra-arterial route is now more than an attempt at saving life; it is the treatment for profound circulatory collapse with loss of arterial pressure. If blood or plasma are not readily available, the knowledge that some substitutes are of value may be of help Successful use of polyvinylpyrolidine and gelatine have been reported during the past year (175, 176).

Oxygen therapy, in order to be effective, must be based upon a sound knowledge of the underlying pathology of the condition for which it is being used, no less upon the effects of anoxia and adequate oxygenation on the tissues of the body, and also upon the physical methods of the administration undertaken Otherwise, it is not only wasteful but may also be harmful. For an excellent survey, the reader is referred to the work of Comroe & Dripps (177).

The equipment of all postoperative recovery rooms will no doubt include a tracheotomy set, the early use of which in the prevention of pulmonary complications in severely ill patients with respiratory difficulty is wisely advocated (178 to 181).

Mention has been made by Papper (182) and also by a Danish correspondent (183) commending the contribution that expert resuscitation can make to the treatment of barbiturate poisoning. Very often the cases are still sent to medical and psychiatric wards

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Infant (184), the authors of this chapter feel warranted to mention again. This volume forms the basis of any medical approach to the infant. Concerning the techniques adopted and drugs advised in pediatric anesthesia for different types of surgery, reference is made to the foregoing article and to a number of others of which lack of space prevents discussion (155 to 162). The summarized views expressed therein lay stress upon the preoperative psychological approach and biochemical assessment, upon the maintenance of anesthesia during which the infant or child is actively and methodically helped through the operation, and upon the careful postoperative study until physiological equilibrium has once more been gained.

Obstetrical anesthesia.—The divers effects of various analgesic and amnesic drugs upon the pains of labor, upon the birth mechanism, and upon the fetus continue to be assayed. A combination of morphine and meperidine has been stated to produce satisfactory analgesia much resembling that brought about by heroin. The latter drug is still in frequent use, however, when allowed. Another combination, one stated to have minimal effect upon the fetus, is scopolamine and meperidine. The time most dangerous for the fetus for the administration of morphine is said to be 2 to 3½ hr., and for that of meperidine 1½ hr., before birth (163 to 166).

Reports concerning the anesthetic management of the delivery reveal the increasing popularity of conduction anesthesia. Spinal anesthesia of the saddle block variety with dibucaine (Nupercaine) or tetracaine are in extensive use. Andros & Priddle (167) state that they are very satisfied with this method after three years' trial. Caudal anesthesia and pudendal block have been noted to give excellent results, but no large series has been reviewed this year.

A study of the fall in arterial pressure in pregnant women who received a "high selective spinal" suggests the state of dilatation of the pelvic blood vessels and pressure of the gravid uterus are responsible for this phenomenon (168).

General anesthesia with nitrous oxide or trichloroethylene has been reported on extensively in the United Kingdom and there are a few accounts of the use of the latter on the American continent.

Maternal deaths following aspiration of vomitus during general anesthesia in the United States have been analyzed by Merrill & Hingson (169), who enumerate precautions to be taken against this disaster. Works published about the anesthetic management of Caesarean section, although advocating conduction anesthesia or light general anesthesia aided with a relaxant drug, do suggest that the management of such a case really depends upon the reason for the Caesarean section. Potter & Pender (170) state the interesting trends in their work since 1936 with respect to this condition.

Concerning abnormal obstetrics, Bryce-Smith and his associates (171) have considered the question of the importance of uterine tone in protection of the placenta during the manipulation of external version. They doubt the wisdom of the time honored use of deep inhalation anesthesia and instead have used thiopental, Flaxedil, and nitrous oxide combination. In their

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RADIOLOGY[1]

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The radiological literature of the past year is stimulating evidence of the high interests of the physicians practicing in this branch of medicine There has been further co-ordination in such diverse disciplines as engineering, physics, mathematics, chemistry, illustration, radiobiology, physiology, and pathology for the welfare of the patient.

The most difficult aspect in formulating this review is to indicate trends of the future based upon current developments. Certainly in the field of radiodiagnosis one is impressed with the changes being wrought by electronics, the increasing possibilities for accurate diagnoses, and the need for the radiologist to exhort his medical colleagues aggressively to pursue minimal or possible signs of malignancy. The field of radiotherapy has yielded no cure-all for cancer, but the long term statistics are narrowing down the treatment methods in favor of those giving the highest yield. Extremely high voltage techniques are showing promising advantages for highly selected patients and are in fact suggesting the division of therapy patients into two groups. The first will be those who have a chance of cure. Their problem will be individually attacked by a team of radiation specialists closely rivaling in number those one sees assembled for a major surgical procedure. Their weapons will be fantastic and financially difficult to underwrite or maintain at first The second group will be those whose malignancies have spread considerably or are of low radiation sensitivity. They will continue to be palliated, perhaps to an even greater degree than at present as the newer techniques progress. The segregation into groups should be a further challenge to early diagnosis

Radiodiagnosis

Heart and great vessels.—The injection of contrast media into the vascular channels continues to offer an important diagnostic approach in problem cases An excellent review of the literature, development of equipment, techniques, indications, limitations, and pertinent findings in angiocardiography have been presented by Scott (1) in the Carmen Lecture of the Radiological Society of North America. He felt that this procedure is applicable to about half of the cardiac structural problems, that congenital heart defects are better understood as a result of this type of work, and that integrated rapid serialized film units are most helpful. Celis, Pacheco & del Castillo (2) stated that angiocardiography is the method of choice in differentiating aortic aneurysms

[1] The survey of the literature pertaining to this review was concluded in September, 1951, and does not include radioactivity.

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ly and have found useful visualization of the abdominal aorta. They presented three cases.

Angiography and aortography techniques all stressed patient sensitivity tests to the contrast media being used. The effect of one of these media, sodium iodomethamate (Neo-Iopax), on the heart has been studied by direct writer electrocardiographic recordings during the examination by Zinn, Levinson, Johns & Griffith (12). Immediate ischemic changes were shown by inverted T-waves. Irritable ventricular foci with frequent and prolonged bursts of ventricular tachycardia were frequently observed, but the onset was delayed and the duration may be as long as 30 min. after the injection. Quinidine or procaine amide given prior to the examination appeared to minimize the dangers. Retrograde aortography gave fewer cardiac manifestations because smaller concentrations of dye reached the myocardium. Gordon, Brahms, Megibow & Sussman (13) have studied the effect of Diodrast on the cardiovascular response of dogs. Seventy per cent dye injected rapidly caused an increase in arterial pressure, pulse pressure, and venous pressure of a short duration. A fall was subsequently observed in all these elements and electrocardiographic changes were noted. The effects were a little less marked with more dilute dye and eliminated with slow injection. These effects, as well as those to be discussed in connection with cerebral angiography, in no way minimize the usefulness of these injection procedures. They do, however, warrant careful selection of patients and evaluation of possible information to be gained from the risk.

The clinical manifestations of advanced vascular disease in our aging population were presented by Zeman & Schenk (14). They feel that local or diffuse calcific deposits in the vessels of older patients should not necessarily be considered as the cause of functional changes Many of these lesions exist without symptoms In a review of 200 chest films on patients over 60 years of age, 9 5 per cent showed no change in heart or aortic contour or density. Others showed varying degrees and combinations of elongation, widening, calcification, and enlargement Aortic dilatation reduces systolic and to a lesser degree diastolic pressure. This dilatation may counterbalance increased peripheral resistance or decreased aortic elasticity. Calcified deposits in the aortic valve are an important clue in establishing the diagnosis of aortic stenosis A calcified mitral annulus fibrosis should be looked for in a heart block, and evidence of coronary artery calcification, myocardial infarction, and cardiac aneurysm anticipated in older patients.

Respiratory tract —Solitary areas of necrosis of the lung are losing their significance as probable indicators of benign pathology. Wigh & Gilmore (15) have reviewed 160 cases of bronchogenic carcinoma, and they report 22 per cent of them as showing single or multiple necrotic lung areas. Ten per cent of their cases with solitary areas of necrosis turned out to be due to neoplasm. A reversal is occurring in the ratio of abscesses from carcinoma and simple necrosis This may be due in part to the use of antibiotics. The importance of cancer as a cause of abscess after the fourth decade of life

from other mediastinal tumors. Roberts, Dotter & Steinberg (3) have studied superior vena cava and innominate veins by angiocardiographic methods After determining length and width of the dye shadows in normal subjects, abnormalities were expressed in terms of the variations. Fifty-five patients having obstruction were found to have tumor in 78 per cent and aneurysm in 15 per cent of the examinations The others were due to mediastinitis or thrombosis.

In addition to the various rapid serial film devices discussed by Scott, others have appeared during the year. Thompson, Figley, & Hodges (4) have described their device utilizing 11-in. wide film for exposures as fast as 4 per sec. Baron (5) has developed a simplified mechanism using 10 cassettes of the 10×12-in. size, which should appeal to the smaller institution.

A most pertinent editorial by Neuhauser (6) stressed the inadequacy of any device or modality at solving any problem related to angiocardiography. He feels that the radiologist must have all the pertinent facts of history, physical examination, and laboratory findings in order to make a reasonably sound diagnosis. For example, an x-ray diagnosis of patent ductus arteriosus should not be made without the presence of a heart murmur consistent with it. Ventricular enlargement is easier to diagnose than hypertrophy from the roentgen film, but knowledge of the electrocardiographic evidence makes the x-ray diagnosis of ventricular hypertrophy much more accurate. Angiocardiography has contributed greatly to our understanding of congenital defects of the heart, but it is not a simplification of them or their diagnosis

Ruskin & Samuel (7) have stressed plain film findings of a curvilinear calcification in some patients with patent ductus arteriosus Anomalous vascular trunks associated with congenital cardiac abnormalities are prone to atheromatous calcifications. This calcific shadow occurs between the aortic and pulmonary shadows and at operation is found on the aortic side of the ductus. Slightly overpenetrated and coned down films help to bring out this significant diagnostic clue. Stauffer, Labree & Adams (8) have identified the azygos vein by catheterization and revealed decrease in size of the vein in changing from the recumbent to the upright position, and during increased intrathoracic pressure. These changes help to differentiate the vein shadow from an enlarged lymph node.

Schorr, Dreyfuss & Schwartz (9) have shown the value of the recumbent right anterior oblique position for barium swallow in picking an early and possibly the earliest sign of left auricle enlargement.

There is revived interest in visualization of the abdominal aorta and its main branches by aortography. Sante (10) presented a good review of this work, the preparation of the patient, and the technique for visualizing [illegible] to the abdominal organs By demonstrating the quantity-

tion of renal ischemia, renal cysts, renal neoplasms, and placenta previa Leigh & Rogers (11) injected 70 per cent iodopyracet (Diodrast) intravenous-

the coarseness of metastases. They cleared in five days. About 20 per cent coalesced into sublobular areas of consolidation. These patients were quite ill, but clearing occurred in 10 days if cavitation did not follow secondary invasion, in which case clearing averaged 10 weeks. Another group comprising about 17 per cent of the total showed a lobar consolidation which lacked a uniform density and disappeared in 20 to 30 days. A presumptive diagnosis of influenzal pneumonia may be justifiable at the height of an epidemic, but the findings so closely mimic tuberculosis, pnemuoconiosis, and metastases that real certainty can never be achieved.

Feldman (22) described a case of localized interlobar pleural effusion in heart failure and included an excellent summary of the literature. While this ovoid or elliptical shadow may be mistaken for several more serious diagnositic possibilities, its relation to the fissure line shadow is important in diagnosis.

Loeffler's syndrome (eosinophilia, transient pulmonary infiltrations, and paucity of symptoms) is described in two year old twins for the first time. Schechter & Graub (23) treated their patients with corticotropin (ACTH) successfully, and listed an imposing group of conditions which are possibilities in the early differential diagnosis.

Lubert & Krause (24) have studied the mechanisms and roentgen patterns of lobar collapse. They stressed the point that the appearance of the lobe changes from a three-dimensional to a two-dimensional triangle which is often flattened along the mediastinum or parietal pleura Hanelin & Eyler (25) discussed five cases of pulmonary artery thrombosis and one or more peripheral thrombosis. A consistent finding was a reduced distention during life of pulmonary vessels distal to the thrombus. The location of the large thrombi coincided with the altered hilar contour noted on the chest films

Arendt (26) has reviewed a series of patients finally diagnosed as infectious mononucleosis. Interestingly, they were referred to the radiologist as cases of pharyngeal edema, virus pneumonia, appendicitis. cholecystitis, leukemia, lymphobastoma, malaria, brucellosis, and colitis Although there are no specific roentgen findings, hilar adenopathy sometimes preceded enlargement of peripheral nodes, and lung markings sometimes suggested virus pneumonia.

Silverman (27) reviewed the significance of pulmonary calcifications. Histoplasmosis, as well as tuberculosis, can result in calcifications The former is much less fatal than previously supposed and, with a skin sensitivity test available, greater consideration should be given to correct identification of these densities.

Gastrointestinal tract—Ruzicka & Rigler (28) have shown the value of individualizing upper gastrointestinal examinations by inflating the stomach during certain stages of the barium meal. It is particularly helpful in differentiating polyps from giant rugae, giant rugae from carcinoma, and in assessing relative pliability of the gastric wall.

Duodenal ulcers are being detected with increasing frequency in younger

is reemphasized. Freedlander, Wolpaw & Mendelsohn (16) summarized their experiences with 18 patients with asymptomatic intrathoracic growths Exploratory thoracotomy is a relatively harmless procedure and may be the only method for diagnosis and eradication of malignancy in an early stage. They were impressed with the extent of disease in some patients without symptoms, and feel that watchful waiting or ill-advised x-ray therapy is hazardous.

Healy (17) has analyzed 19 cases of bronchogenic cysts. Symptoms were not noted until growth had reached pressure producing stages These occurred between the ages of 18 and 51 years. The cyst was ovoid in shape in 18 of the 19 cases, and a change in contour between inspiration and expiration films was helpful in suspecting the diagnoses in some cases.

Lemon & Good (18) admitted the difficulty in diagnosing hamartoma of the lung preoperatively. They have reviewed 17 cases surgically explored in the last six years at Mayo Clinic. Eleven of these lesions revealed no calcification to help in the x-ray diagnosis. In only five cases were the findings suggestive enough to include hamartoma as a possibility or probability in the differential diagnosis preoperatively.

Pulmonary adenomatosis appears in two separate reports. King & Carroll (19) showed four cases. This is a relatively rare disease of unknown etiology. There is proliferation of alveolar lining cells throughout large areas of the lung, but there are no invasive tendencies or metastases The symptoms are progressive dyspnea, cough productive of large amounts of thin mucoid sputum, weakness and weight loss; the result is fatal. By x-ray there are widespread discrete and confluent poorly outlined nodular densities but no hilar adenopathy. Serial films show progression. Paul & Juhl (20) reported four additional cases with similar findings and course.

Endemic influenza is usually not serious and few radiologists ever see many complications of it. The epidemic form of influenza shows increasing virulence and infectiousness over the endemic form and complications are more frequent Harrison (21) has had an opportunity to see many radiographic appearances of its pulmonary complications in a large general hospital in the northwest area of England. Pneumonia is the most common complication and is more apt to be due to secondary invaders in a weakened patient than to the virus itself. These secondary pneumonias seem to come on after a short interval of recovery from the initial infection. True influenzal pneumonia diagnoses must rest on isolation of the virus and serological tests or on the basis of subjective complaints during an epidemic. The white blood count is normal or lowered in influenzal pneumonia. By x-ray there are four groups of appearances. At one or both bases, 35 per cent showed multiple small areas of infiltration, suggesting a bronchiolitis The areas were larger than those seen in miliary tuberculosis and had soft, ill-defined edges. They cleared in 5 to 10 days. In 25 per cent these small infiltrations were shown throughout both lung fields, although one lung often showed more involvement than the other. The shadows varied from miliary sizes to

flattening or narrowing distally, coarsen or efface folds on the pancreatic side, flatten the valvulae conniventes, deform the bulb or antrum of stomach on the posterior or greater curvature side, widen the duodenal sweep, cause undue retention of barium, or cause the deficiency type of small bowel pattern, or ileus. Wasch & Epstein (39) have reported their work in evaluating Monophen [2-(4-hydroxy-3,5-diiodobenzyl)-cyclohexane carboxylic acid], a new gall bladder dye. In their experience it seems to have the desirable characteristics of previously used media and in addition yields fewer undesirable side reactions.

Genitourinary tract.—Robbins, Colby, Sosman & Eyler (40) have made an extensive investigation of the comparative advantages and disadvantages of Diodrast over the more recently developed sodium acetrizoate (Urokon). Approximately 3,000 examinations were used, and no significant differences in diagnostic quality were observed. Sodium acetrizoate was excreted a little more rapidly than iodopyracet and there were many more vasomotor reactions with iodopyracet. Minimal reactions were about equal with both dyes. Rapid injection of concentrated iodopyracet or sodium iodomethamate to obtain a nephrogram has been reported by Weens, Olnich, James & Warren (41) and by Vesey, Dotter & Steinberg (42). This type of examination has been an aid where the more conventional pyelograms are diagnostically inadequate, in physiological studies, in renal circulation, and in differentiating renal and extrarenal masses. Windholz (43) has made a very detailed study of the central or peripelvic fat tissue of the kidney. Its visualization and recognition enables one to outline better the inner aspect of the kidney parenchyma. This makes possible more minute detection of disease. Owen (44) summarized the experiences of joint conferences between radiology and urology in the proper interpretation of roentgenograms. They were able to correlate x-ray and surgical findings in at least 95 per cent of cases. Radiographic examinations were particularly helpful in the diagnosis of deformities of the renal tract, hydronephrosis, tuberculosis, neoplasm, calculi, and various postoperative conditions X-ray examinations were of little value in pyelitis, pyelonephritis, cystitis, or detection of prostatic disorders.

Holmes (45) has reviewed 18 primary neoplasms of the ureter seen at the Massachusetts General Hospital in the last 20 years Seventeen were carcinomas, and one was hemangioma Hematuria was the outstanding feature in all of the cases and other features were either failure to excrete dye or to excrete into a dilated renal pelvis and ureter on the affected side Retrograde pyelography gave the greatest information

Thumann & Randall (46) have used cystourethrography to considerable advantage in evaluating diseases of the prostate gland They feel that it is less painful and less traumatic than cystoscopy and the film gives a permanent record.

Bergin (47) raises a great many possible objections to salpingography but shows that in actual practice most of these are not valid. He feels that Diodine Viscous (a diethanolamine salt of diiodopyridine with 6 per cent

age groups. Alexander (29) has found 30 instances of duodenal ulcer in examining 254 children between the ages of 2 and 14 years Twelve were girls, and 18 were boys. Children do not present the pain-food-ease syndrome so commonly seen in adults but do have nausea, vomiting, and some vague abdominal pain. It is essential to demonstrate the niche, but eccentricity of the bulb is not seen in children. In a still younger age group, Lemak (30) observed 18 cases between 1940 and 1949 in patients under two months of age who came to autopsy with gastroduodenal ulcerations. The diagnosis was not often made clinically and contrast media probably would not have demonstrated the ulcerations because they were so superficial. The diagnosis should be suspected in a newborn with hematemesis or melena, especially if prematurity and brain damage are also present. The x-ray findings are most often associated with perforation or absence of gas in small bowel and colon, if pyloric stenosis and atresia can be excluded.

Barsh (31) admitted that small bowel malignancies are rare, but more are being picked up with improving technique. An important observation is that carcinoids do not give blood in the stool, but carcinomas do. Small intestinal patterns are greatly influenced by the type of opaque medium used. Adrian, French & Mucklow (32) have used meals of simple and complex suspensions of barium and noted different patterns even in the same patients. A flocculated deficiency pattern is best brought out by use of a simple suspension of barium, and maximal mucosal detail by a complex nonflocculating suspension. Zimmer (33) has demonstrated the differences in the intestinal picture with different brands of barium products and stresses the need for standardization.

Jones, Kaplan & Windholz (34) have used a colloidal suspension of barium sulfate for air-contrast studies of the colon. The detail of the colon picture is excellent, and is in part due to the thorough cleansing of the bowel before examination. Positive findings are checked in one week by a repeat examination Kirsner, Palmer & Klotz (35) presented 24 patients whose x-ray manifestations of ulcerative colitis have been either completely reversed or markedly improved. Patients who successfully negotiated the first attack seemed to deal with subsequent recurrences in an increasingly effective manner. They stressed the importance of the total regime of treatment and hint that current work with ACTH is most encouraging.

Sharpe & Golden (36) have studied 42 patients for changes in the appearance of end to end anastomosis following partial resection of the colon. Of these, 93 per cent showed some abnormality at some time, but the less significant defects gradually diasppeared on serial examinations.

The incidence of gallstones which float is higher than generally appreciated. Elsey & Jacobs (37) believe that a film with the patient in the upright position should be more commonly used The x-ray diagnosis of pancreatitis has been reviewed by Gottlieb, Dorfman & Cregg (38). They reported nine cases in which encroachment may make it difficult to fill a segment of descending duodenum, narrow the same area, dilate the same area but add

Martin (57) has applied geometry to hip joint architecture and finds that any asymmetry indicates a mechanical unbalance and underlying joint abnormality. He considers the two hip joints as mirror images of each other. Variations in contours are easier to detect by use of geometric angles This early detection may help to minimize the complicated and prolonged surgery so often required at later stages of the same diseases.

The extent of bone involvement by neoplasm or inflammation required for x-ray detection is amazing. Ardran (58) found on working with autopsy specimens of vertebrae, that a 3-mm. hole drilled lengthwise could barely be detected in the lateral projections and not at all in the anterior posterior projections. When the hole was filled with water to simulate soft tumor density, visualization was not possible by x-ray. In fact the hole had to be enlarged to 14 mm. in order to be suspected This accounts for the large number of secondary bone deposits discovered at autopsy and not detected by x-ray.

Manning (59) discussed hemangioma of the vertebrae and presented three cases with symptoms The x-ray diagnosis is usually an incidental finding in routine work, and about 10 per cent of autopsy findings indicate a previously unsuspected hemangioma X-ray therapy is useful in the symptomatic cases, but surgery has to be used if there is sudden compression of the spinal cord caused by collapse of the bone.

Coley, Higinbotham & Groesbeck (60) reviewed 37 cases of primary reticulum-cell sarcoma of bone. The lack of a specific roentgen change makes certain clinical features helpful in suspecting the correct diagnosis. The disease occurs twice as often in males as females; well over half of the patients are in the second and third decades of life with a mean age of 33.7 years; 65 per cent occur in the long bones with 79 per cent of these occurring in the lower extremities; pain is the initial symptom, and swelling and disability ensue. The lesion arises in the medullary portion of bone and is predominately destructive, although later it may become slightly productive. The growth is largely confined within bone and has an ill-defined border. The treatment is dictated by the fact that surgery results in prompt appearance of multiple metastases. X-ray therapy through multiple ports with a tumor [illegible] se is more benign than other [illegible] There are 48 per cent 5-year, [illegible]

Solovay & Gardner (61) have examined 57 patients with Marie-Strumpell arthritis and found 13 with complete fusion of the manubriosternal joint. Their figures show the joint fused in 23 per cent of cases of this disease and 5 per cent of cases of other types of involvement.

Hoecker & Roofe (62) have studied the deposition of radium in two human patients. The distribution is not uniform, and an osteogenic sarcoma in one of these patients contained negligible amounts of radium. Calcium, but not radium, was mobilized in these cases, and they suggested that the two may not be biochemically similar.

Soft tissue.—A remarkable series of radiographic lesions of the breast are presented by Leborgne (63) The technique gives unusual detail to normal

polyvinyl alcohol) overcomes many of the difficulties attributed to iodized oil (Lipiodol) in this particular field of use.

Central nervous system.—Two articles in the field of cerebral angiography cover the mechanical aspects, normal anatomy, and possible pathological demonstrations of this method. Scott & Seaman (48) presented a great deal of background for this work, and Curry & Culbreth (49) have brought out the normal anatomy to a very understandable degree in their presentation Falls, Bassett & Lamberts (50) have observed ocular complications following intracranial arteriography. In 80 consecutive patients, 35 had cutaneous, 65 conjunctival, and 20 retinal petechial hemorrhages. Pupillary dilatation, optic neuritis, angiospasm of retinal vessels, and blindness were also observed The cause is not known but a combination of allergic, toxic, or physical factors seems most likely.

Abrodil (sodium salt of monoiodomethane-sulfonic acid) is a water-soluble contrast medium particularly good for myelography and, by better filling of nerve roots, gives additional diagnostic clues according to Lange & Odegaard (51).

Camp (52) has studied the significance of intracranial calcifications in relation to neoplasm of the brain. In differentiating well-known nonneoplastic calcifications, he stresses that one considers whether the location is on or in the brain, and unilateral or bilateral. The diagnosis can be more accurately predicted by increasing knowledge of the characteristics of the calcification.

Osseous.—The manifestations of hypervitaminosis A are causing considerable confusion, particularly in the differential diagnosis of infantile cortical hyperostosis. Caffey (53) pointed out that the hypervitaminosis A cases lack the facial swellings and mandibular hyperostoses seen in infantile cortical hyperostosis. The onset is also usually later in the vitamin cases. He presented seven patients whose excessive vitamin intake occurred several months before the symptoms, which appeared between the 6th and 15th month of life. The symptoms were tender swellings, pruritis, anorexia, hyperirritability, and limitation of motion. The swellings were deep and related to the periostitis. Rineberg & Gross (54) reported a similar case in a child 33 months old. Hypervitaminosis D was described in five cases by Christensen, Liebman & Sosman (55). The metastatic calcifications occur so widely in tissues and so inconsistently that there is no valid x-ray criterion. During the active stage of poisoning, there is generalized osteoporosis as well as metastatic calcification, particularly in synovial cavities, bursae, tendon sheaths, and other periarticular structures These changes may be confused with chronic nephritis, hyperparathyroidism, and tumoral calcinosis. Holt (56) discussed vitamin D resistant rickets and presented six cases. This is a hereditary form of late rickets which is not associated with visceral disease. These patients are dwarfs, have severe deformities, hypophosphatemia, and respond well to large doses of vitamin D. The roentgen changes are marked even in the presence of ordinarily adequate intake of the vitamin and the dangers of corrective procedures during active stages of the disease are stressed.

of life or certainly useful life. All of these benefits do not occur in one patient or uniformly in groups, but the net result is usually some degree of relief or improvement.

A comparative report on the effects of roentgen ray and steroid hormone therapy in mammary cancer which has spread to bone has been made by Garland, Baker, Picard & Sisson (69). Pain is relieved in about 70 per cent of the patients by x-ray, and the duration is from 50 to 100 per cent of their survival time. The hormone-treated groups experienced relief of pain in 40 to 75 per cent of cases, but the duration of relief seemed to be less than with x-ray. Survival time, recalcification of metastases, and minimization of complications or side effects were all in favor of x-ray. Simultaneous irradiation and steroid hormone therapy does not seem as much indicated as serial use when indicated according to the authors. A subsequent report of the Subcommittee on Steroids and Cancer of the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association (70) indicated that radiation therapy is preferable to hormones for most soft tissue and bone metastases from breast cancer. However, for lung lesions, and very widespread soft tissue and bone lesions, hormone therapy seemed more applicable. Nathanson (71) and Stoll (72) were in general agreement with many aspects of these reports also. Collins (73) has improved dose distribution to primary breast cancers by building up breast contours with bolus material so that a cube results with the nipple area, central axis and chest wall areas receiving a more uniform dosage. Portmann (74) presented a classification of breast cancer which more clearly determined the indications for and limitations of different therapeutic procedures. He advocated postoperative roentgen therapy when axillary nodes are found to be involved by tumor, and primary roentgen therapy when patients presented more than one criterion in his classification Along a similar line, Bloom (75) felt that a combination of histological grading and clinical staging would overcome some of the fallacies of present systems This system helps to explain some of the difficulties in comparing results of patients treated with surgery alone and in combination with x-ray. Stein, Costolow & Meland (76) joined the crusade for uniform classifications and feel that postoperative x-ray is indicated if axillary lymph nodes are proven to be involved by cancer at surgery.

The treatment of cancer of the cervix has been evaluated by Schmitz (77) His evaluation was prefaced by a review of a recent survey of 77 medical schools for the type of treatment administered to Stage 1 cancer of the cervix Only 1 3 per cent of them reported use of surgery alone An analysis of 188 cases of primary cancer of the cervix treated by the author has been presented The over-all cure rate was 43 6 per cent at the end of five years. Using 800-kv. x-ray the doses at points A and B in the pelvis were 3,500 r each, and radium dosage was 7,000 gamma roentgens at point A and 1,540 gamma roentgens at point B. Nolan & Du Sault (78) reported 55 per cent five-year survivals when the dosage was more than 7,000 gamma roentgens

and especially to abnormal tissues in the breast. The sharpness of the margins of a density, the trabecular pattern, and type of calcification are utilized diagnostically. This type of examination adds some information to that obtained by palpation, but in no sense is specific. He stressed that carcinomas may exist without film evidence of their presence.

Miscellaneous.—How much radiation dosage the patient receives during an x-ray examination has been quite reliably determined and charted by Sorrentino & Yalow (64) and by Handloser & Love (65). The dosage charts provide a quick answer to this problem of increasing importance. A single x-ray exposure of the hand results in an air dose of .027 r while that for a lateral spot film of the lumbar spine is 10 r. Doses delivered to other areas and quick methods of calculating doses under varying conditions are included.

The increasing number of ways in which lost surgical sponges are radiopaquely identified is almost confusing in itself. Levene (66) in conjunction with Bauer and Black Research Laboratories, Chicago, has developed a vulcanized radiopaque in one corner of the sponge. This area is of sufficient size, characteristic pattern, and density to prevent its being hidden by adjacent bone density, or being missed as a result of moderate variations in x-ray penetration.

The use of roentgenograms for identification of disaster victims is gruesomely presented by Singleton (67), based upon the Noronic disaster. The importance of having previously made films available for anatomical comparisons stresses the importance of long-term storage of the original x-ray films or at least microfilming all previous identification possibilities on our population.

Radiation Therapy

Unfortunately no one form of therapy is the answer to cancer, but certainly radiation therapy is called upon at one time or another in the course of most of those cancers which are not eradicated at the first attempt by whatever method is used. This, plus the fact that over 50 per cent of cancers are not early when first subjected to treatment, gives radiation therapy a load of predominately advanced or hopeless patients The results are therefore misleading if one tries to define them in terms of tables or estimates of longevity. Widmann (68) stressed that the results on the hopeless cases alone would warrant the survival of radium and roentgen therapy even in the presence of a drastically effective agent against early cancer. His extensive observations emphasized the importance of such palliative results as improvement in health and strength, gain in weight, relief of pain and discomfort, regressions and even healing of ugly fungating ulcerations, lessening or controling hemorrhage, healing of pathological fractures or other metastatic evidences in bone, suppression of cough and dyspnea in lung and mediastinal neoplasms, slowing of rate of spread, and often by a prolongation

too often are not uniform enough in penetration as applied to give the desired homogeneous effect in the several millimeters of lymphoid tissue involved. Localization is often poor, and all in all overdosage is frequently so excessive to some layers that severe late complications are predicted The ability to treat total areas of involvement uniformly without discomfort and obtain good results with a minimum of dosage with roentgen therapy more than offsets the inconvenience of spaced treatments or the occasional transitory swelling of the parotid glands which follows irradiation through this zone Jacox (84), in an editorial on the nasopharyngeal applicator, stated that the tissue surface in contact with the radium applicator receives 4,440 equivalent roentgens, but 3 and 4 mm away, the dose is only 696 and 432 r. X-ray therapy for the same conditions through 6 by 8 cm. fields externally yields a more uniform dose to a larger volume and is therefore more apt to be anti-inflammatory as well as destructive of excessive lymphoid tissue The total depth dose is 865 r in divided doses over a period of three weeks Kramer (85) reported on 54 cases of nasopharyngeal cancer, 26 of which had cervical lymph node involvement at the time they were first examined for therapy When nodes were involved, 52 were treated by x-ray therapy locally and regionally. The five-year cure rate was 25 per cent. Transitional cell cancer carried the worst prognosis, and eradication of the disease with the first course of treatment was essential. He noted that the majority of difficulties arose during the first two years after treatment, and that any patient surviving three years without evidence of recurrence or spread had a good prognosis Peirce & Bouchard (86) showed an increase in survival time for glioblastoma multiforme but not for astrocytoma Following surgery, a depth dose of at least 7,500 r was used for the former and 9,000 for the latter Their glioblastoma multiforme patients showed an average survival of 15 6 months with combined treatment, while those of Penfield showed only 8 5 months' average survival after surgery. Freid & Davidoff (87) reviewed their experience chiefly with single protracted courses of postoperative radiation therapy at 200 kv and 400 kv. and felt that the preferred method of radiation and what constituted adequate dosage were still unsolved problems. Their best results were with primary cerebellar sarcoma, cerebellar astrocytomas, and cerebellar medulloblastomas; moderate benefits were noted in cerebral astrocytomas with larger doses, but no conclusive benefits were observed in spongioblastoma polare or glioblastomas Leddy & Marshall (88) have reviewed 108 cases of pituitary adamantinomas (craniopharyngiomas) seen at Mayo Clinic between 1916 and 1947. Although this tumor is commonly associated with the earlier years of life, 47 per cent of their cases were over 20 years of age. By roentgenogram, 56 per cent showed calcific deposits, and 77 per cent showed microscopic evidence of calcium. X-ray therapy was not used as much in the earlier cases as the more recent ones, so only 15 patients could be evaluated in this respect. Two-thirds showed definite relief related to this therapy. The suggested therapy scheme is 1,500 r tumor dose with 200-kv. x-ray followed by 1,350 r additional depth

at point A in the pelvis, 38 per cent five-year survivals when the dose was less than 7,000 gamma roentgens at point A. Untreated cases showed less than 5 per cent five-year survival. Buschke & Cantril (79) evaluated radiation treatment of carcinoma of the vagina and presented 10 cases, six being alive and well 3 to 6½ years after treatment. They felt that the previous poor prognosis in such cases was due to insufficient external irradiation. They advocated radical external x-ray in view of the rich lymphatics of the vagina and low histologic differentiation of tumors, and supplemental radium. They used six fields with 200-kv. x-ray and four fields with 800-kv. x-ray. Radium was applied as ovoids.

Cancer of the ovary has been discussed by Kerr & Elkins (80), and was based largely on experience in treating 168 proven cases. They suggested use of a classification slightly different from Heyman's and recommended postoperative x-ray therapy to all patients outside of Group 1, which is adequately treated by complete removal of the primary and any visible metastases. They were not able to show any additional benefit of postoperative irradiation to Group 1 cases. The best prognoses in the other groups were for pseudomucinous and papillary cystadenocarcinomas with five-year survivals of 46 per cent and 42 per cent respectively. The authors feel that in the case of papillary cystadenocarcinoma a five-year survival is not a reliable indicator since an additional 20 per cent die of the disease later. Solid carcinomas yielded only 16 per cent five-year survivals.

Kaplan, Cohen & Roswit (81) reviewed 158 cases of malignant testicular tumors treated between 1933 and 1948 Following local surgery they delivered 2000 r depth dose with 400-kv. radiation to the deep lymphatic pathways for seminomas and 3,000 r to other types. They have found a 34 per cent over-all three-year survival with the extremes being 46 per cent with seminomas and 11 per cent with choriocarcinomas They, like many others, expressed the feeling that the three-year survival is the critical period for good prognosis.

Flocks (82) has analyzed 540 bladder cancers treated between 1932 and 1942. While removal or destructive methods of treatment other than radiation were used in the majority of cases, he felt that irradiation helped in some cases, although he was not impressed with it as a sole means of destroying a bladder tumor. Some of the difficulties were admittedly due to inability to apply a uniform adequate dosage to all portions of the tumor. He suggested high voltage therapy in selected cases prior to partial or total cystectomy in order to seal off some of the pathways of spread.

The nasopharynx has been the site for much discussion this year as to treatment methods and dangers. *Garland, Hill, Mottram & Sisson (83) have* discussed the relative advantages and disadvantages of roentgen and radium therapy for lymphoid hyperplasia, particularly as related to deafness and allied disturbances. While both methods effect reduction in lymphoid tissue, there are many dangers and misconceptions connected with one or the other forms of treatment. Radium offers a high intensity source of rays which

sis on deep damage to normal tissues. It is true that deeply situated tumors can be killed with these powerful machines but considerable remains to be determined regarding time-dose and tolerance relationships. Twenty cases were studied in detail for tolerance dose to the adult male colon. The colon dose in the mildly damaged ranged from 4,176 r in 47 days to 6,100 r in 74 days. The severely damaged group had doses ranging from 5,952 r in 63 days to 6,750 r in 61 days In the autopsy cases where bowel change contributed to death, the local dose was over 6,000 r.

At the higher level of 2,000,000-v x-rays Hare and co-workers (98) have confirmed the skin sparing effects of radiation of this degree of penetration, and the bone sparing advantages predicted by Spiers (99). The additional technique of rotating the patient with the tumor centered in the path of this high-powered beam further increased the distribution advantages of this radiation The technique is so complicated that more of a technical staff is required than is commonly available in x-ray departments. However, in larger treatment centers, highly selected patients should receive additional benefits from this combination These higher voltage techniques all call for very precise localization of the tumor, and the results of treatment at lower voltages might be improved if greater time were spent on this aspect. Love, Combs, Askew & Harcourt (100) have discussed techniques for localization which involve lead wires for transfer of body contours, wax models, and paper charts

Progressing to the 23,000,000-v. level, Johns (101) and Harvey, Haas, Laughlin, and their associates (102 to 105) have found still further evidence of superficial tissue sparing, greater deep concentration, and still greater depth penetration of dose. The preliminary observations indicated that treatment at this level was not only practical but advantageous for certain localized deeply located tumors The work was admittedly in early stages and the authors emphasized the fact that the advantages are other than a new or different biological effect of the particular x-rays being used.

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dose three months later. The greatest mortality is at surgery. Of those surviving surgery, 46 per cent are alive five years or more later, while of those given postoperative x-ray 83 per cent are alive five years later.

Irradiation for hormonal control of advanced cancer is a complicated field. Murphy & Schwippert (89) have been irradiating the pituitary gland for additional palliation in advanced cancer of the prostate gland. Orchiectomy is known to offer some benefit in this condition apparently by altering the chemical environment of the host. At the same time the anterior lobe of the pituitary enlarges and its hormone output increases. The normal pituitary gland is known to be quite resistant to radiation therapy, and even after large doses gradually returns to normal. It was therefore suggested that repeated courses of treatment be given. Their depth doses varied from 756 r in 12 days to 4,860 r in 35 days, and survival figures while improved were not necessarily related to the larger doses.

The ability of the newer drugs to combat infectious conditions is apparent by the lack of significant new reports of the use of radiations for these conditions. Inflammatory conditions which respond to radiation therapy are favorably reported by Richmond (90) for ankylosing spondylitis, Steen & McCullough (91) for supraspinatus tendinitis, and Leucutia (92) for osteitis pubis.

A symposium on blood and lymph node tumors by Wright (93), Hoster (94), and Morton (95) indicated continued support for roentgen therapy in chronic leukemia, Hodgkin's disease and lymphoblastoma. It should be stressed that nitrogen mustard plays an important role in conjunction with x-ray in Hodgkin's disease and that there continues to be a dangerous tendency to withhold nitrogen mustard too long or at least until roentgen resistance is manifest. Nitrogen mustard is most useful in widespread cases, when local recurrences follow in the same area of recent x-ray irradiation and in certain abdominal involvement where it is difficult to estimate the extent or accuracy of direct x-ray therapy. X-ray is preferable in superficial or palpable involvements, also in the mediastinum and lungs when infection is not a complicating factor.

An attempt to evaluate the work now going on in the field of supravoltage radiations calls for a definition of limits and dosage units. The work of the last 15 years or more with 1,000,000-v. x-ray machines has shown their benefits to be due to increased depth dose rather than to a different type of action of their rays. Murphy & Reinhard (96) have compared 1000-kv., 400-kv., and 200-kv radiations clinically. Patients treated with small daily doses to each of four ports a day showed less immediate and late reactions than those treated with a larger dose to one port per day. The changes appeared to be greater with 200 kv. than the higher radiations. They felt that their results in cancer of the cervix were better with the higher voltage but admitted the possibility of increased bladder and rectal complications as a result of the greater penetration. Amory & Brick (97) have reviewed the cases treated with the 1,000-kv. machine at Walter Reed Hospital with particular empha-

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RADIOACTIVITY

Effects of Whole Body Irradiation[1]

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Radiation through its biologic effects and its use as a tool in research is rapidly spreading into all facets of science and medicine. Through the medium of the atomic bomb, radiation is extending into the fields of diplomacy, politics, and the social sciences Since medicine reaps the profits of research in all fields and since newer weapons of warfare increase the heavy burden of the practice of medicine, it is logical and proper that the profession should take an active role in the painful adjustment of society to the realities and potential acute and chronic hazards of nuclear explosions. Accordingly this review will consider the physiologic effects of single whole body radiation on mammals, the modification of the biologic response by various agents given before and after irradiation, and the application of these findings to the treatment of casualties in atomic warfare Papers on cellular physiology and radiation chemistry are only occasionally referred to Their value for the ultimate understanding of the nature of radiation injury is fundamental. However, to date, the gap between our knowledge of cellular physiology and of the clinical syndrome remains largely unbridged. We have attempted to include primarily those papers which have advanced our present concepts of the clinical manifestations of radiation injury. A complete list of references alone would fill the entire allotted space.

Dose Measurements and Lethal Dose

The roentgen "r," a measure of the ionization in air, does not measure the dose absorbed by the tissue At the 6th International Congress of Radiology in London (1950) an International Commission for Radiological Units (122) recommended "that the dose be expressed in terms of the quantity

[1] This review covers the period from January, 1950, to September, 1951 Occasionally, earlier articles are considered It is regrettable that much of the data collected during the war under the auspices of the Manhattan Engineering Project for development of the atomic bomb, though declassified, remains in government documents Much of this is accessible through the Technical Information Service, U. S Atomic Energy Commission, Oak Ridge, Tennessee.

[2] Opinions and assertions are those of the authors and do not necessarily reflect those of the U. S. Naval Service.

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response. This has been well demonstrated by the studies of Karnofsky *et al.* (88, 91) and Stearner (147, 148) in chickens and Brunst *et al* (19) in Triton (salamander).

Survival Time and Clinical Syndromes

The correlations of dose to survival time has been reinvestigated by Quastler *et al.* (121) and Cronkite (34). Quastler *et al.* (121) demonstrated that in mice uniformly lethal doses of 1,200 to 12,000 r lead to an acute "intestinal" syndrome and death in 3½ days, which can be reproduced by irradiation of the eventrated gut. The hyperacute syndrome at doses of over 12,000 r, which is accompanied by neuromuscular symptoms and leads to death in a few hours, can be reproduced by irradiation of the head with comparable doses. This confirms earlier work that at least three different mechanisms of death must be considered, resulting respectively from bone marrow injury, intestinal injury, and brain injury. The direct brain injury occurs only at extremely high doses. The intestinal injury occurs below the LD_{100}, accompanied by injury to lymphoid and hemopoietic tissue, leading to two peaks of mortality (69). In rats these peaks occur at approximately five and eleven days. Bond *et al.* (13) showed that shielding of the abdomen abolished the first peak, and shielding the rest of the body prevented the appearance of the second peak The clinical course following whole body radiation in man as observed in Hiroshima and Nagasaki (99, 115) was frequently complicated by thermal burns and mechanical trauma, but here again at least two phases of morbidity and mortality were recognized. Deaths during the first two weeks were preceded by continuous anorexia, vomiting and diarrhea, fever, and finally coma or delirium, while patients that presented milder initial symptoms of a few days only had a symptom-free interval until the appearance of epilation at two weeks, followed by ascending temperature, purpura, necrotizing pharyngitis, gingivitis, and frequently sanguineous diarrhea Death occurred about two weeks after the onset of the fever. The time relationship of the two peaks of mortality in man thus differs from that observed in laboratory animals, especially since the second peak reached its maximum only at the end of the first month, This may well be a result of a difference in the biologic response of man and of laboratory animals. It is also possible that the particular circumstances of the bombing, partial shielding of the body, or the characteristics of bomb radiation influenced the shape of the mortality curve in the Japanese

Intestinal Injury: Early Phase

The intestinal injury is a characteristic histologic feature of the early phase of radiation injury, affects the small bowel primarily, and is repaired rapidly. Barrow & Tullis (6) studied the gastrointestinal tract in mice after exposure to 1100 r, a uniformly fatal dose for mice. Epithelial damage was extensive, but regeneration was almost complete by 80 hr. In the rat, Metcalf (106) found regeneration complete 60 hr. after an approximately midlethal

of energy absorbed per unit mass (ergs per gram) of irradiated material at the place of interest." Since this quantity is not readily determined by direct measurement, practical adoption of the recommended units awaits the preparation of satisfactory conversion tables. The Commission further recommended that the roentgen be retained as the unit of measurement of x- and γ-rays. The conditions under which the dose is measured should be designated free in air, at skin surface, or at *x* cm. depth, and the data such as scatter, half-value layer, distance, and kvp included. In commenting on the Commission's recommendations, Failla (60) stated that

> no physical unit can fulfill the ideal requirements of making all biological effects of ionizing radiation appear independent of wave length or more generally, independent of specific ionization . . . (In) the present state of our knowledge no chemical or biological unit can fulfill the ideal requirement either.

For the purpose of correlating dose with effects on the whole body, depth dose and distribution of the absorbed energy become of great importance, as shown by Tullis *et al.* (160) on swine. Jaeger (89) notes that no single physical unit can satisfactorily express the total dose effect because of differences in relative absorption by different tissues. In view of these difficulties, it is considered essential to express the dose biologically as well as physically when trying to correlate effect with dose Preferably, the biologic measure of the radiation used should include the LD_{50} and the slope of the dose-mortality curve, as in all toxicological studies In this review, we have indicated, wherever possible, the dose in r and the mortality response (sublethal, per cent mortality, or supralethal).

Newell (113) surveyed "33 presumed experts in regard to tolerance of man for larger doses of radiation (x-rays or gamma rays) over the whole body." Opinions varied so greatly that it appears unlikely that useful information will be obtained short of human experimentation or the military use of the atomic bomb. Extrapolation from animals to man is a highly questionable procedure because of the previously mentioned dose difficulties and because of the variation between species. A recent summary of the available estimates of the LD_{50} of laboratory animals with 200 kvp gives 200 r for the guinea pig, 500 to 600 r for the rat, 600 r for the LAf_1 mouse, and 800 r for the rabbit (155). The dose in r can serve as a rough guide only, because techniques of irradiation and strains of animals influence the LD_{50}. Methods for exposure of animals to x-rays are reported by Hagen *et al* (70) and Chapman *et al.* (24). Abrams (1) has presented evidence that suggests that age profoundly influences radiosensitivity in mice. Mortality was low when irradiated at one and fifteen days, high at thirty days, and thereafter susceptibility decreased with increasing age. Sex and weight did not appear to influence radiosensitivity except insomuch as weight reflected age

While the radiosensitivity of different mammalian species varies considerably, the biologic response shows considerable similarity Nonmammals show very wide variation both in the percentile lethal dose and biologic

absorptive capacity and permeability of the small bowel was unchanged after irradiation, and that some apparently contradictory earlier findings may be explained on the basis of the altered motility of the bowel.

A number of metabolic changes have been described during the early phase of radiation injury. DuBois (51), using Potter's method of blocking of metabolic pathways with fluoracetate, found a marked inhibition of citrate synthesis in the spleen and thymus in rats exposed to 400 r and a lesser inhibition after exposure to 200 r. Recovery began early and was complete by fourteen days after irradiation with 200 r, but was delayed with larger doses. Kidney, ileum, pancreas, and testes were likewise affected, but not brain and heart. Du Bois points out that interference with the reactions of the Krebs cycle is a likely, but not the only, explanation for these findings Du Bois also demonstrated that livers of irradiated male rats accumulated citrate after fluoracetate treatment, in contrast to the inability of normal male rats to do so. Since female rats normally accumulate citrate after fluoracetate treatment, steroid hormones may possibly be involved in the production of this effect. Ross & Ely (129) report that glycogen accumulated in the livers of rats fasted 24 hr. before and after whole body irradiation, while glycogen was virtually absent from the livers of fasted controls. Shielding of the liver did not prevent glycogen accumulation, suggesting that the effect was not a result of primary liver cell damage. Histologic evidence of direct damage to liver cells has been demonstrated by Warren *et al.* (163). The adrenal may also be injured by whole body radiation, since shielding of the adrenals significantly protected rats, particularly from the early mortality (53) This does not appear to rule out the existence of an indirect effect on the adrenal, which has been confirmed by Ross & Ely, who found a significantly greater increase in the adrenal weight of fasted irradiated rats compared with fasted control rats, although the adrenal was shielded (129). Several papers have dealt with indirect evidence suggesting an initial increase in adrenal activity after irradiation The subsequent response was variable (55, 92, 140, 162).

A variety of changes in plasma constituents have been recorded during the first few days after exposure to lethal doses of radiation. In one Japanese report low chloride levels were reported in man. This was expected because of early vomiting and diarrhea In rats, which cannot vomit, Kohn (95) found that plasma chlorides are only slightly diminished during the first two days after exposure and moderately increased on the third and fourth day, particularly with higher doses, when diarrhea occurs There was a concomitant decrease in erythrocyte chloride, and the total blood chlorides stayed fairly constant. Results in guinea pigs were comparable. Bowers & Scott (15) found an early potassium loss from the cells and later an increase in cellular sodium in rats after exposure to LD_{50} and higher doses Painter & Cooley (116) found the water balance to be shifted in opposite directions in different tissues Supplee *et al* (151) and Storey, Wish & Furth (150) point out that slight changes in the concentration of blood constituents must be interpreted with consideration of the total plasma and cell volumes

dose. Brecher & Cronkite (16) studied the regeneration of early small bowel lesions in dogs after whole body irradiation of 300 to 3,000 r. The LD_{50} was about 350 r. After 2,500 or 3,000 r dogs died on the third or fourth days and severely damaged epithelium of the small gut showed no evidence of regeneration. After doses of up to 1,000 r the microscopic appearance of the small bowel returned to normal within about four days. Superficial erosions of the gastrointestinal tract which occurred after the first week were not restricted to the small bowel and appeared to be secondary to the very common mucosal and submucosal hemorrhages. As a rule these lesions did not progress to deeper ulceration and bacterial invasion. However, bacterial invasion was seen in tonsillar lesions in agranulocytic dogs dying after the first week. In man, atypical epithelial cells in the stomach and small bowel were present on the fourth day which was the earliest available human material (99). Ulcerative lesions were not observed before the seventh day. One patient showed both bizarre epithelial cells and focal necrosis of the mucosa and submucosa on the eleventh day. After the second week, no abnormal epithelial cells were found. Necrotic agranulocytic and hemorrhagic lesions were now frequent in the large bowel, gums, and tonsils, and occurred only *rarely in the small intestine. We believe the evidence indicates a different* pathogenesis for the early and late lesions of the alimentary tract The early lesions are restricted to the small bowel and are the results of direct injury to the epithelial cells. The later lesions appear to be sequelae of pancytopenia (agranulocytic infections and hemorrhage). In man and dog the *late lesions are uncommon in the small bowel, the site of early epithelial injury.*

The evidence strongly suggests that injury to the small bowel is responsible for the early deaths after lethal doses of radiation. However, the exact mechanism of death is not understood Conard (30) recorded the contractility of the exposed gut of the rat and found the tone and motility *of the jejunum increased within 1 min. after doses as low as 100 r.* This finding is of great general interest because of the short latent period. Propulsive motility was accelerated during the first hour after 800 r and tended to decrease below normal from the third hour to the third day, after which it returned to normal Changes in tonicity and motility were also reported by Mead (105) and Bennett (8) who followed the absorption of fat and protein in mice exposed to 600 r, a dose above the LD_{50} The emptying time of the stomach was markedly delayed 2 and 24 hr. after irradiation, presumably as a result of increased tone of the pyloric sphincter, but the passage of nutrients through the small gut was accelerated At 2, 24, and 96 hr after irradiation absorption of the portion of fat and protein that actually reached the small gut did not differ significantly from normal Reduction in total absorption at 2 and 24 hr. appeared to result from the delay of food reaching the small gut and the accelerated passage There was no evidence of large molecule absorption (I^{131}-tagged protein molecules) Absorption of vitamin A was normal or increased in rats on the second to sixth day after exposure to 600 r, a midlethal dose [Bennett *et al* (7)] This series of data thus suggests that the

creased progressively during the first 11 days after exposure to an LD_{60}. Subsequent observation showed a return to normal except in very anemic animals. Serum iron was elevated during the first day in rats exposed to doses from 10 to 1,500 r, but did not remain elevated except in animals exposed to doses above 500 r. The authors suggest that there is an interference with normal iron metabolism. We believe that suppression of erythropoiesis during the first week or two may play a major role, because iron released by the normal attrition of red cells is not reutilized and therefore accumulates in the spleen and liver. Richmond, Altman & Solomon (126) determined hemin synthesis in homogenates of bone marrow from rabbits exposed to 800 r, a midlethal dose. Hemin synthesis was reduced 48 hr. to three weeks after exposure and was slightly above normal levels at four weeks. These findings followed generally the known sequence of suppression and recovery of erythropoiesis, but, surprisingly, hemin synthesis was found to be increased five-fold immediately after radiation Changes in oxygen uptake followed a similar curve, but globin synthesis did not While the increased hemin synthesis after irradiation recalls older ideas of an immediate stimulating effect of radiation injury, a subsequent paper of Richmond, Altman & Solomon (125) establishes the fact that the capacity for hemin synthesis is not an indication of actual erythropoiesis. The spleen of rabbits exposed to 800 r showed an increase in hemin synthesis throughout the four-week observation period, although during most of this period only very few erythropoietic centers were discernible histologically in the spleen.

The occurrence of a maturation arrest in man after acute radiation may be inferred from the observation of reticulum cell hyperplasia in the marrow of the Japanese exposed to nuclear radiation (99, 115).

Abnormal cell forms in the peripheral blood of rabbits after midlethal doses have been described and illustrated by Jacobson (84). These included giant platelets, fragmentation or split nuclei of lymphocytes, giant multilobed polymorphonuclear cells, and a number of apparently distintegrating cells which were difficult to classify. They were generally seen during the early phase of rapid development of neutropenia. Similar cells were seen in the rat by Rosenthal (128) who also linked them to the degenerative phase of bone marrow damage. No abnormal forms were found after the twelfth day when recovery began. A frequently mentioned feature of the recovery phase is macrocytosis (84, 102) Since the reticulocytes which are numerous at this time have a larger volume than mature red cells, the macrocytosis might be expected.

ANEMIA

It has been known for some time that the postirradiation anemia is frequently much more severe than could be expected from the cessation of

In rats (151), rabbits, and mice (150) these authors found an initial drop of the plasma volume during the first few days after irradiation with midlethal or higher doses. A subsequent rise in the plasma volume kept the total blood volume fairly constant in spite of a progressive decrease in the cell volume, which was presumably a result of suppression of erythropoiesis. Soberman, Keating & Maxwell (144) measured electrolytes, water balance, plasma volume, and hematocrit in dogs after exposure to midlethal doses which produce only minimal or no clinical symptoms during the first week. The only consistent changes found were a gradual decrease in the hematocrit and red cell volume and an increase in plasma volume. Kohn (95, 96) collected extensive data on nonelectrolytes in the plasma following midlethal doses in rats and guinea pigs. The more striking changes include a 50 per cent increase in blood sugar and cholesterol during the first three to four days and a spurious increase in the A/G ratio which could be traced to an abnormal ether-extractable plasma constituent. NPN and phosphorus levels were also elevated. In rabbits, an elevation of the blood sugar two to four hours after midlethal doses was reported by Thompson & Steadman (159). Kohn (96) also investigated the influence of immaturity, adrenalectomy, and hypophysectomy on the plasma changes in rats The results do not as yet indicate the chain of events that lead to the observed changes and only point to the number and complexity of radiation injuries to various tissues and compensatory reactions which are only secondarily reflected in the level of plasma constituents.

Bone Marrow Injury

The sequelae of bone marrow injury dominate the picture of the second phase of radiation injury which is characterized by hemorrhage, infection, and anemia. The bone marrow of rats exposed to a midlethal dose of radiation has been studied by Rosenthal (128) and Metcalf (106). In conformity with previous studies on other species, there was a rapid and almost complete suppression of erythropoiesis and granulocytopoiesis, and a slower decline in number of megakaryocytes. Plasma and reticulum cells were prominent in the depleted marrow. Recovery of erythropoiesis was seen in the marrow before regeneration of the granulocytic series and megakaryocytes The conclusion that erythropoiesis recovers more readily than granulocytopoiesis is supported by the work of Valentine *et al.* (161) in cats given a sublethal dose of 200 r. Liebow *et al.* (99) questioned the sensitivity of the erythroid series to radiation in man because at autopsy islands of erythropoiesis were frequently present in the marrow despite extreme atrophy of the remainder of the tissue. Valentine's and Metcalf's work now suggests that erythropoiesis, though readily suppressed by radiation, recovers relatively rapidly and this may explain the findings in man The early suppression of erythropoiesis has been confirmed indirectly by the decrease in the iron uptake of red cells with the use of a tracer technique [Hennessy (74)]. Ludewig & Chanutin (23, 103) report that the iron content of the spleen and liver in-

was out of proportion to the thrombopenia and that bleeding occasionally occurred when the platelet count was in the normal range. In addition these workers believed that toluidine blue and protamin intravenously stopped bleeding while the platelets remained low, thus indicating that bleeding resulted from some factor other than thrombocytopenia. Cronkite (32) found the coagulation defect inconstantly in the Bikini animals. In some the clotting time was decreased by toluidine blue titration. The thrombocytopenia was marked. Minute amounts of thromboplastin and thrombin clotted the blood quickly. Rosenthal & Benedek (127) found no evidence for heparinemia in the rabbit and ascribed bleeding and the faulty coagulation to thrombocytopenia. Their failure to find a prolonged whole blood clotting time is not surprising, since blood was taken by cardiac puncture Whole blood clotting times are reliable only when done under the most meticulous circumstances on venous or arterial blood to prevent contamination by tissue juices Further work by Allen (4) and Jackson *et al* (80, 81) has shown that the correlation of prolonged clotting time to thrombocytopenia is invariably present when meticulous technique is adhered to. The concept of "heparinemia" as a cause of radiation hemorrhage was re-investigated by Cronkite *et al.* (44) and by Jackson *et al* (81) and no evidence for the presence of anticoagulants of heparin-like type was found. Holden *et al* (75) have considered that "hypothromboplastinemia" is a contributing cause of the hemorrhagic phase of radiation injury and have felt that there was little evidence for the presence of an anticoagulant. Allen *et al* (4) now place less emphasis on the importance of a heparin-like anticoagulant as a cause of radiation hemorrhage and more emphasis on the severe thrombocytopenia. Cohn (29) has studied blood coagulation in the irradiated rat and has concluded that the sequelae of thrombocytopenia are probably the most important factors in producing the tendency to bleed. Jackson *et al.* (80) have demonstrated that the diminution in the utilization of prothrombin is even more closely correlated with the decreasing platelet count than whole blood clotting time. All reports continue in agreement that there is no substantial decrease in prothrombin concentrations (3, 4, 80, 81). Accelerator factors are under study (80) and it has been shown that there is no apparent decrease in accelerator globulin. Reports on serum prothrombin conversion accelerator (SPCA of Alexander), the presence and activity of antihemophilic factor, and the lipid antithromboplastin have not yet been published

Direct evaluation of this platelet factor in radiation hemorrhage by *in vitro* and *in vivo* studies were delayed because methods for separation of the intact platelet in relatively pure suspensions were not available With the development of satisfactory techniques for separation of the platelet by Dillard *et al* (48) *in vitro* and *in vivo* studies were undertaken. The addition of washed platelets and of platelets in plasma *in vitro* to freshly drawn whole blood completely corrects all of the coagulation defects (37). The transfusion of separated platelets in the thrombopenic dog corrects the coagulation defect, returns platelet levels towards normal, and diminishes hemorrhage. The

guinea pigs, by Metcalf *et al.* (106) on rats, and by Bennett, Rekers & Howland (9) in dogs Bennett *et al.* (9) suggest that the frequent infection with hemolytic organisms may account for additional red cell destruction. Bigelow *et al.* (10) cannulated the thoracic duct of dogs and observed a heavy influx of red cells into the lymph beginning with the seventh day after radiation They suggest that endothelial damage is responsible for the flooding of most of the lymph node sinuses with red cells, local erythrophagocytosis and hemosiderosis, and drainage of red cells into the thoracic duct. When red cells were labelled with Fe^{59}, radioactive iron reached its greatest concentration per gram of tissue in the lymph nodes, with smaller but still very considerable amounts present in the spleen and liver (62). Davis *et al.* (47) confirmed earlier observations that no increase in mechanical or osmotic fragility is demonstrable *in vitro* except after exposures to 20,000 r. In an attempt to demonstrate a hemolytic effect of radiation injury *in vivo* Davis *et al.* (47) measured urinary bilirubin in four dogs with renal bile fistulas exposed to 150 to 250 r. Bilirubin excretion was increased either during the first or second week, or both. These authors point out that the increased bilirubin excretion may be a result of destruction of hemoglobinized red cell precursors, absorption of extravasated blood, or diversion of hemoglobin precursors that are not being utilized. In our opinion severe anemia is most likely the result of hemorrhage. An increased rate of destruction of red cells is not yet proved. However, Meyniel & Bazin (107) report changes in the electric charge of mature red blood cells of rabbits seven to fourteen days after exposure to sublethal doses of 400 to 600 r. This abnormality was traced to the protein fraction of the plasma The significance of this observation is not known. However, as the first observation on alterations of the red cell during the period anemia is developing it deserves further study.

Hemorrhage

Hemorrhage in the course of the acute syndrome produced by exposure to whole body irradiation has been recognized for years. LeRoy (98) described the hematology of atomic bomb casualties with an analysis of the factors concerned with hemorrhage in the Japanese casualties from the atomic bomb. The final publication of the full report on the *Medical Effects of the Atomic Bomb* (115) demonstrates by clinical descriptions, photographs of autopsies, etc., that hemorrhage of one sort or another not associated with trauma contributed to the mortality of human radiation casualties. The status of the pathogenesis of the hemorrhagic phase was reviewed by Cronkite *et al.* (45) and the type of hemorrhage seen in the Japanese compared to the hemorrhagic phase of experimentally irradiated mammals.

Allen *et al.* (3) introduced the concept of heparinemia as a contributing cause of radiation hemorrhage. This concept was based on prolonged clotting time, on indirect titration by antiheparin compounds (toluidine blue and protamine), and on isolation of a substance from the blood of four irradiated dogs which resembled heparin. This group felt that the coagulation defect

was out of proportion to the thrombopenia and that bleeding occasionally occurred when the platelet count was in the normal range. In addition these workers believed that toluidine blue and protamin intravenously stopped bleeding while the platelets remained low, thus indicating that bleeding resulted from some factor other than thrombocytopenia. Cronkite (32) found the coagulation defect inconstantly in the Bikini animals. In some the clotting time was decreased by toluidine blue titration. The thrombocytopenia was marked. Minute amounts of thromboplastin and thrombin clotted the blood quickly. Rosenthal & Benedek (127) found no evidence for heparinemia in the rabbit and ascribed bleeding and the faulty coagulation to thrombocytopenia. Their failure to find a prolonged whole blood clotting time is not surprising, since blood was taken by cardiac puncture. Whole blood clotting times are reliable only when done under the most meticulous circumstances on venous or arterial blood to prevent contamination by tissue juices Further work by Allen (4) and Jackson *et al.* (80, 81) has shown that the correlation of prolonged clotting time to thrombocytopenia is invariably present when meticulous technique is adhered to. The concept of "heparinemia" as a cause of radiation hemorrhage was re-investigated by Cronkite *et al.* (44) and by Jackson *et al.* (81) and no evidence for the presence of anticoagulants of heparin-like type was found. Holden *et al* (75) have considered that "hypothromboplastinemia" is a contributing cause of the hemorrhagic phase of radiation injury and have felt that there was little evidence for the presence of an anticoagulant. Allen *et al.* (4) now place less emphasis on the importance of a heparin-like anticoagulant as a cause of radiation hemorrhage and more emphasis on the severe thrombocytopenia. Cohn (29) has studied blood coagulation in the irradiated rat and has concluded that the sequelae of thrombocytopenia are probably the most important factors in producing the tendency to bleed Jackson *et al.* (80) have demonstrated that the diminution in the utilization of prothrombin is even more closely correlated with the decreasing platelet count than whole blood clotting time. All reports continue in agreement that there is no substantial decrease in prothrombin concentrations (3, 4, 80, 81). Accelerator factors are under study (80) and it has been shown that there is no apparent decrease in accelerator globulin. Reports on serum prothrombin conversion accelerator (SPCA of Alexander), the presence and activity of antihemophilic factor, and the lipid antithromboplastin have not yet been published.

Direct evaluation of this platelet factor in radiation hemorrhage by *in vitro* and *in vivo* studies were delayed because methods for separation of the intact platelet in relatively pure suspensions were not available. With the development of satisfactory techniques for separation of the platelet by Dillard *et al* (48) *in vitro* and *in vivo* studies were undertaken The addition of washed platelets and of platelets in plasma *in vitro* to freshly drawn whole blood completely corrects all of the coagulation defects (37). The transfusion of separated platelets in the thrombopenic dog corrects the coagulation defect, returns platelet levels towards normal, and diminishes hemorrhage. The

guinea pigs, by Metcalf *et al.* (106) on rats, and by Bennett, Rekers & Howland (9) in dogs Bennett *et al.* (9) suggest that the frequent infection with hemolytic organisms may account for additional red cell destruction. Bigelow *et al.* (10) cannulated the thoracic duct of dogs and observed a heavy influx of red cells into the lymph beginning with the seventh day after radiation They suggest that endothelial damage is responsible for the flooding of most of the lymph node sinuses with red cells, local erythrophagocytosis and hemosiderosis, and drainage of red cells into the thoracic duct. When red cells were labelled with Fe^{55}, radioactive iron reached its greatest concentration per gram of tissue in the lymph nodes, with smaller but still very considerable amounts present in the spleen and liver (62). Davis *et al.* (47) confirmed earlier observations that no increase in mechanical or osmotic fragility is demonstrable *in vitro* except after exposures to 20,000 r. In an attempt to demonstrate a hemolytic effect of radiation injury *in vivo* Davis *et al* (47) measured urinary bilirubin in four dogs with renal bile fistulas exposed to 150 to 250 r. Bilirubin excretion was increased either during the first or second week, or both. These authors point out that the increased bilirubin excretion may be a result of destruction of hemoglobinized red cell precursors, absorption of extravasated blood, or diversion of hemoglobin precursors that are not being utilized. In our opinion severe anemia is most likely the result of hemorrhage. An increased rate of destruction of red cells is not yet proved. However, Meyniel & Bazin (107) report changes in the electric charge of mature red blood cells of rabbits seven to fourteen days after exposure to sublethal doses of 400 to 600 r This abnormality was traced to the protein fraction of the plasma. The significance of this observation is not known. However, as the first observation on alterations of the red cell during the period anemia is developing it deserves further study.

HEMORRHAGE

Hemorrhage in the course of the acute syndrome produced by exposure to whole body irradiation has been recognized for years. LeRoy (98) described the hematology of atomic bomb casualties with an analysis of the factors concerned with hemorrhage in the Japanese casualties from the atomic bomb. The final publication of the full report on the *Medical Effects of the Atomic Bomb* (115) demonstrates by clinical descriptions, photographs of autopsies, etc., that hemorrhage of one sort or another not associated with trauma contributed to the mortality of human radiation casualties. The status of the pathogenesis of the hemorrhagic phase was reviewed by Cronkite *et al.* (45) and the type of hemorrhage seen in the Japanese compared to the hemorrhagic phase of experimentally irradiated mammals

Allen *et al.* (3) introduced the concept of heparinemia as a contributing cause of radiation hemorrhage This concept was based on prolonged clotting time, on indirect titration by antiheparin compounds (toluidine blue and protamine), and on isolation of a substance from the blood of four irradiated dogs which resembled heparin. This group felt that the coagulation defect

the LD_{100} when both blood transfusion and aureomycin were given, but not from either therapy alone.

Howland (78) reported that irradiated dogs treated with aureomycin show less tendency to hemorrhage and intestinal ulceration than do control dogs, and he suggests that aureomycin "corrects the bleeding tendency." However, no differences in the platelet level or in other coagulation factors have yet been reported. Since infection is known to aggravate bleeding in thrombocytopenic purpura, suppression of infection may well result in less extensive or less numerous overt hemorrhages, without any direct effect by aureomycin on hemostasis. The susceptibility to infection of mice which have been exposed to nonlethal doses has been studied by Shechmeister, Bond & Swift (135, 136). The highest point of increased susceptibility of these mice to infection by *Streptococcus zooepidemicus* occurred on approximately the fifteenth day following exposure. Surprisingly, injection of avirulent or killed *P. pestis* also resulted in deaths from what was otherwise a nonlethal dose. Ingram & Mason (79) reported that the degree of leukopenia after exposure to a given dose is similar in rats that die and rats that survive. The authors conclude that the degree of leukopenia is of no prognostic value in the individual case. This conclusion should perhaps be qualified Ingram & Mason's own data show that both the degree of leukopenia and the per cent mortality are functions of the dose A given degree of leukopenia may well allow us to determine the probability of an individual's survival.

The capacity to form antibodies is markedly impaired after whole body radiation. The entire subject has been reviewed by Taliaferro (157). Recent publications confirm that the antibody response is suppressed following whole body irradiation. In the rabbit, shielding of either the spleen or the appendix prevented the suppression of the antibody response, according to Jacobson (86). Burrows (21) found transient increase in excretion of coproantibody in guinea pigs although serum antibodies were depressed Hollingsworth (76) observed that the disappearance of passively transferred antibody is not affected by prior irradiation of the animal. The suppression of antibody response can be modified by prior injection of horse serum (49) or by post-radiation administration of adrenal extracts (110).

Late Effects

Death from the acute radiation syndrome in warm-blooded laboratory animals seldom occurs after the fourth week In the Japanese, death from the acute syndrome with leukopenia and thrombocytopenia rarely occurred after the sixth week (99, 115). However, anemia occasionally persisted, and patients remained or became emaciated. The Japanese physicians were inclined to consider this peculiar cachexia as a clinical entity. These patients died from pneumonitis or enteritis Some bone marrow regeneration was practically always present at autopsy, and some marrows were hyperplastic. Only a rare case presented agranulocytic lesions. It is not clear how many of

daily transfusion of platelets into the irradiated dog commencing before the thrombopenia develops helps in maintenance of the platelet level and apparently prevents spontaneous purpura.

Investigation of the usefulness of flavonoids in irradiation injury continues. Sokoloff *et al.* (145, 146) believe these substances decrease mortality and diminish bleeding in rats. Cronkite *et al.* (40) have not been able to confirm this in mice.

It is of collateral interest that severe hemorrhage tends to follow the sharp elevation of the rectal temperature (3, 32, 81). This partially corroborates the observations that infection tends to precipitate severe purpura. The diminution of bleeding by antibiotics is discussed in the section on INFECTION.

INFECTION

The role of infection in the course of radiation injury has been the subject of an outstanding study by Miller *et al.* (108, 109) on mice given an LD_{50} or higher dose of radiation. Cultures from irradiated animals were only rarely positive during the first four days after exposure. Thereafter the incidence of positive cultures increased rapidly and paralleled the mortality, which was greatest on the ninth day. The maximum incidence of positive blood or spleen cultures occurred on the ninth and tenth day and amounted to 85 per cent after exposure to 600 r and 54 per cent after exposure to 450 r. All cultures on nonirradiated animals were sterile. Streptomycin or combinations of streptomycin and other antibiotics reduced mortality following radiation injury, except when streptomycin-resistant organisms occurred in the gut of the mice. These studies not only underscore the importance of infection but also implicate the gut as the source of invading organisms in mice. In guinea pigs, Burrows (20) reported blood stream invasion by hemolytic streptococci or staphylococcus aureus in 8 of 15 animals dying from exposure to an LD_{50} The mode of invasion was not investigated. Furth, Coulter & Howland (65) reported on the increased incidence of positive blood cultures in irradiated dogs. The role of exotoxins from massive growth of bacteria in agranulocytic lesions has not been assessed. Such lesions, reminiscent of those in human agranulocytosis, occur in the tonsils of almost all dogs dying from lethal doses of x-ray, according to Brecher & Cronkite (16). Similar but more extensive and sometimes hemorrhagic lesions were found in the Japanese exposed to bomb radiation (99, 115) Failure of aureomycin and polymyxin to reduce mortality from radiation injury in the rat has been reported (63). Terramycin reduced the mortality only slightly. It may be suspected that the invading organisms were not sufficiently susceptible to the three antibiotics used. Since the onset of mortality was occasionally delayed in these experiments, development of resistant strains may also play a part (63, 78). Aureomycin and terramycin were reported by Howland *et al.* to reduce mortality in dogs, after exposure to an LD_{60} (63, 77). Allen (4) found a reduction in mortality after doses slightly above

MODIFICATION OF RESPONSE

Pre-irradiation factors —Bond *et al.* (12) reported that pre-existing disease in rats increases mortality from irradiation. Endemic infections in a rat colony also increased mortality. This may have resulted from "activation" of a latent infection or increased susceptibility to infection after irradiation. Such factors may have been in part responsible for the high incidence of late diarrhea in those exposed to nuclear radiation in Japan, where dysenteric disorders are common. In animals diarrhea is not marked except during the first week. Protein depletion before irradiation strikingly increased the susceptibility to irradiation (90). Cronkite *et al.* (41, 43) have shown that adrenalectomy increases the sensitivity to radiation. Induction of anoxia prior to irradiation and maintenance during the irradiation period increases the survival rate [Limperos (100); Dowdy *et al* (50)]. Anoxia induced by *p*-aminopropiophenone (PAPP) methemoglobinemia is also effective [Storer *et al.* (149)]. Sodium nitrite methemoglobinemia was not effective, hence, PAPP may have some additional action other than the methemoglobinemia anoxia Protection of mice by methylene blue [Hall (73)] may result from methemoglobinemia or from its ability to function as an oxidation-reduction system. Cyanide, which interferes with utilization of oxygen, was found effective by Bacq (5). Dowdy *et al.* (50) found cyanide ineffective and concluded that there must be an actual decrease in oxygen tension in the tissues in order to show a protective effect. A number of reducing substances have been tested Many sulfhydryl compounds have been found to increase survival rate, e g , cysteine and glutathione [Patt *et al.* (118a)], glutathione [Chapman (25); Cronkite (41, 46)], thiourea[3] [Limperos (101); Mole *et al* (110a)], and dimercaprol (2,3-dimercaptopropanol; BAL) [Works (164)] Forssberg (61) has shown that local injections of cysteine will protect the hair follicles from local irradiation. Hibernation in the marmot [Smith *et al.* (138)] seemed to prolong survival time and lessen the severity of the initial reaction. Haley *et al.* (72) have presented evidence that induction of hypothyroidism or hyperthyroidism before irradiation does not significantly change the mortality rate Earlier work of Blount & Smith (11) indicated increased mortality after induction of hyperthyroidism Shielding of various organs during irradiation significantly increases the survival rate, as shown by shielding the spleen in mice[4] [Jacobson *et al.* (85)], the abdomen [Bond *et al* (13)], the adrenals [Edelman (53, 54)], extremities, liver, lungs, abdomen, and head (2, 66), thus conclusively confirming much earlier work Graham *et al.* (68) confirmed that estrogens and horse serum injected 10 days before irradiation reduced mortality. Exposure of mice to three sub-

[3] The protective effect in this case results from the sulfhydryl groups and not from the antithyroid effect. See references (71) and (72).

[4] The mouse spleen normally contains varying amounts of erythropoietic and granulopoietic tissue and megakaryocytes Hence, shielding of the mouse spleen qualitatively differs from shielding of spleens that contain only lymphoid elements.

these deaths after the six weeks should be classified as "acute radiation syndrome." However, the number of these cases is small and the majority of those that survived beyond the sixth week made an apparently complete recovery from the acute syndrome.

Late effects are now being studied on the survivors of the atom bombing in Japan. The incidence of cataracts is definitely increased (27, 28). The incidence of leukemia is still being studied. Late effects in laboratory animals include cataracts (26), decreased life expectancy, and increased incidence to tumors (114). In parabiotic rats which survived an otherwise lethal dose of radiation, the weight of the irradiated animals remained consistently below that of its nonirradiated litter mate for many months (17).

Radiation damage to the mouse testes after sublethal doses has been studied histologically in great detail by Eschenbrenner & Miller (58). Mitotic division of spermatogonia ceased for three weeks following irradiation. However, maturation to spermatocytes, meiotic division of spermatocytes and their development to spermatids and spermatozoa continued, and spermatozoa did not completely disappear until the end of the fourth week after exposure. With the dose used, recovery of spermatogonia began during the fourth week and spermatozoa reappeared at six weeks. These observations agree well with older ones that sterility does not develop in mice until two to four weeks after irradiation. In man, hypospermia and azoospermia were found in many of those examined ten weeks after exposure to the nuclear radiation (115). Impotence did not result. No final evaluation of the incidence of recovery or permanent sterility is available as yet

The problem of genetic changes in both germ plasm and somatic cells has been reviewed by Muller at a symposium on Radiation Genetics held in 1948, brought up to date and published in 1950 (112). The comments of Wright (165) written in December, 1949, appear as appropriate today as then: "There are such enormous gaps in our knowledge that no judgement of the genetic consequences (of whole body radiation) in man can be taken very seriously." Muller (112) also emphasized the difficulties in attempting to [illegible]

ations, but some of the descendents were completely sterile. No new evidence has been presented on the incidence of mutations from matings after recovery from temporary sterility. Injurious effects on the fetus are now being investigated in mice [Russel *et al* (131)] The embryo is particularly sensitive to developmental changes in characteristics which are labile in the particular strain, e.g., the number of presacral vertebrae. In the postnatal period, irradiation may interfere with the normal development of growing teeth [English & Tullis (57)] and bone [Montag (111)].

exert their beneficial effect by neutralizing some of the products of irradiated water (free radicals, peroxide, etc.) However, Patt *et al.* (119) state their data "do not support the concept of direct or indirect competition by cysteine for oxidizing radicals."

Histologic and hematologic studies point to the accelerated recovery of the bone marrow as the main feature of spleen shielding[6] and sulfhydryl protection Irradiation with portions of the body shielded is not whole body irradiation and should not be considered as comparable to it. However, Jacobson's spleen shielding experiments have led to the use of spleen transplants after whole body irradiation. Jacobson *et al.* (83, 87) feel that in both instances the evidence favors, but does not prove, that a humoral factor is involved rather than cellular "colonization" They point out that the shielded spleen is often completely infarcted, yet bone marrow regeneration is accelerated The transplanted spleen is only revascularized after apparent disintegration of the splenic cells and "regeneration in the bone marrow from osteoblasts and reticular cell transformation is striking." Patt (118), on the basis of peripheral blood studies, suggested that sulfhydryl compounds lessen the destruction of bone marrow cells by radiation. Cronkite *et al.* (38, 42) found in glutathione-treated animals that the depletion of the bone marrow is not noticeably affected but that recovery is hastened The authors suggested that sulfhydryl compounds may not protect bone marrow cells as such, but rather that they may protect a mechanism necessary for the maturation and differentiation of radioresistant primitive mesenchymal cells. Cronkite and Brecher state that their experiments do not prove the existence of this mechanism, because the histologic methods are not sensitive enough to exclude a slightly greater survival of radiosensitive bone marrow cells in the glutathione-treated animals.

A humoral mechanism, if it exists, could also be responsible for the accelerated bone marrow regeneration and increased survival of rats with postradiation parabiosis [Brecher *et al.* (17)] and of dogs given exchange transfusions [Salisbury *et al.* (132)]. However, in each of these experiments in which bone marrow regeneration was accelerated by postradiation procedures to the irradiated animal, the possibility cannot yet be excluded that transplanted cells rather than a humoral factor initiate the earlier bone marrow recovery in the treated animal.

ATOMIC WARFARE

The attitude of authors on atomic warfare has changed from the defeatism of 1945–46 to one of constructive plans in preparation for atomic war if forced on the democratic world. The complex administrative and medi-

[6] Jacobson *et al.* (82, 83, 87) state that spleen shielding and spleen transplants also accelerate recovery of the gastrointestinal tract However, their observations only indicate a lower incidence of agranulocytic lesions, presumably as a result of early bone marrow recovery. Evidence for an accelerated recovery of the early epithelial injury was not presented

lethal doses of x-ray followed in thirty days by an LD_{40} increased the survival rate of mice (39).

Postirradiation factors.—Smith & Smith (137) showed that moderate exercise only slightly decreased the survival rate of mice. Strenuous exercise in the form of forced swimming after irradiation increased the mortality rate strikingly in rats [Kimmeldorf *et al.* (93)]. Smith & Smith (139) presented evidence showing that induction and maintenance of the hyperthyroid state and administration of dinitrophenol after irradiation for the full observation period increased the mortality. Antithyroid therapy with thiouracil and propylthiouracil did not influence the mortality rate. Ellinger (56) reports that testosterone proprionate administered in daily doses of 0.25 and 0.5 mg to mice after irradiation with an LD_{40} increases the mortality rate. Graham *et al.* (67) studied influence of various adrenal hormones after a single dose of radiation. Results were inconclusive, and it was concluded that radioresistance is not mediated through the adrenal. Smith *et al.* (141) concluded that adrenocorticotropic hormone (ACTH) and cortisone do not increase survival rate and that ACTH after irradiation may be harmful. Larkin (97) presented evidence that administration of atropine after irradiation improved the survival rate of mice. The increased tonicity of the bowel (30) after irradiation may be relevant to this observation. Induction of pregnancy appeared to improve the chances of recovery in dogs [Rekers (123)]. Vitamins do not appear to increase survival from radiation injury. Cronkite *et al.* (33) reported folic acid of no value in lethal radiation injury of swine. Carter *et al.* (22) found that vitamin B_{12} had no effect on the leukopenia induced by irradiation. Sokoloff *et al.* (145, 146) report that a flavonoid (vitamin "P") improves the survival rate of irradiated rats. Cronkite *et al.* (40) with the same flavonoid could not duplicate this protection in the irradiated mouse. Antibiotics of various types given to different species increase both survival time and rate. This is discussed in detail in the section on INFECTION. Rekers (124) and Talbot *et al.* (156) attempted to influence the mortality and clinical course by transplantation of bone marrow into dogs and rats. Results were inconclusive. Transplantation of spleens [Jacobson *et al.* (87)] into mice increased the survival rate. Cross circulation in dogs [Salisbury *et al.* (132)] and parabiosis in rats, accomplished after irradiation [Brecher & Cronkite (17)], favorably influenced radiation injury.

MECHANISMS OF PROTECTIVE ACTION

Reduction of the oxygen tension in the radiosensitive tissues is almost uniformly effective in reducing radiation injury. The current belief that a portion of the effects of ionizing radiation (153) is produced by the products of irradiation of water (peroxide, etc.) makes the beneficial effect of reduced oxygen tension plausible. Haley *et al.* (71) suggest that the failure of the hypothyroid state to increase radioresistance is compatible with this concept, because lowered metabolism diminishes oxygen utilization without affecting the oxygen saturation of the tissues. *Sulfhydryl compounds may*

II. Severe cases (exposure range not well established). Nausea and vomiting occur on day of bombing but last usually less than 24 hr. A symptom-free period follows, during which objective signs of injury are lymphopenia and fluctuating granulopenia. Any time up to the twentieth day the individual may become seriously ill and develop epilation, purpura, oropharyngeal ulcerations, bloody diarrhea, fever, infection with breakdown of wounds and burns, or generalized sepsis. Death occurs in approximately 50 per cent, with sepsis or hemorrhage dominating the pathologic picture.

III Mild to moderately severe cases (radiation exposure not well established). Vomiting is unlikely on day of bombing. During next two weeks no definite symptoms are seen. After two weeks, one or a few of the symptoms seen in the severe cases may appear. The classifications of Cronkite and Dunham are essentially the same because the segregation is based largely on observed symptoms.

Distance from the bomb and personnel radiation dosimeters are of value but cannot supplant the clinical diagnosis of the severity of radiation injury (35) It is pointed out that sensitivity to radiation follows well-known toxicologic laws and the absolute sensitivity of any individual can never be known. Therefore a reading on the personnel radiation dosimeter is not an absolute index of survival. It will assist in establishing the lethal range. The most important function of the dosimeter is the provision of measurements of sublethal radiation for the correlation of dose with long-term effects. Dunham *et al* (52) and Cronkite (34, 35) point out the limitations of clinical laboratory procedures in the diagnosis and prognosis of radiation injury. In general, leukocytes below 500/mm^3 and complete absence of platelets indicate a fatal outcome. A return of platelets, a reticulocytosis, and leukocytes remaining over 1,500/mm^3 indicate but do not assure survival.

The pathogenesis and treatment of the acute syndrome is covered by various authors (4, 14, 34, 35, 52). All authors are in agreement that therapy should be directed at maintenance of acid-base equilibrium, treatment of anemia and infection, and control of the hemorrhagic state. Since the acute radiation syndrome is in many respects like acute pancytopenias from other causes, there is uniformity in opinion as to its management However, there is a difference in opinion in respect to the handling of the hemorrhagic phase Allen *et al.* (4) believe that antiheparin agents (toluidine blue and protamine sulfate) will be of benefit. Dunham *et al* (52) and Cronkite (34, 35) question the value of these agents. The practical clinical management of this syndrome is summarized by Dunham *et al.* (52).

Snell *et al* (142) presented a two-year follow-up on blood studies of the Japanese known to have suffered radiation injury At this interval no significant differences from the control cities had appeared Dunham *et al* (52) now report that it appears as if the incidence of leukemia will be greater. Other late changes such as cataracts are discussed in an earlier section

cal logistic problems other than those concerned with radiation injury cannot be reviewed except by listing recent valuable reference material. The physical destruction on typical structures, the shielding [illegible]

[illegible] logistic problems of mass burn injury and proposes practical mass care The National Research Council symposium on thermal injuries (152) covers experimental and clinical aspects of the subject

A realistic appraisal and evaluation of the effects of atomic weapons is that of Cooney (31). At a symposium on radiologic defense (154), sponsored by the American College of Radiology, the practical aspects of atomic warfare were considered.

Civil defense plans and administration in catastrophes are considered by Schade (134) In addition the American Medical Association is sponsoring a series of articles on disasters of all types. Those connected with atomic [illegible]

[illegible] (62).

The blood picture of atomic bomb casualties is covered by LeRoy (98), based on personal studies in Japan with the Joint Commission. The statistical analysis shows a good correlation between hematologic changes and symptomatology. Unfortunately data are not available for the first 10 days after the bombings and there are insufficient serial studies on the same individuals, hence the pattern of response is based on the trends in exposure groups Cronkite (34, 36) classifies the potential radiation injuries into two categories: the superficial radiation burn from beta rays, and the syndrome of acute radiation injury from exposure of the whole body to penetrating rays The former type of injury is unlikely with the effective strategic use of the bomb. The nature and long-term surgical treatment of radiation burns is covered in detail by Knowlton *et al.* (94) and Brown *et al.* (18).

The diagnosis and segregation of casualties with the acute radiation syndrome has been covered by Cronkite (34, 35, 36) and Dunham *et al* (52). Cronkite proposes that an exposed population be divided into three categories on the basis of the likelihood of survival. Group I: survival improbable (supralethal exposure); Group II: survival possible (the lethal range); Group III: survival probable (sublethal exposure). This type of classification is helpful from the standpoint of medical care given to those groups in which survival might reasonably be increased by intensive treatment. Dunham *et al.* (52) classify radiation injury on the basis of clinical severity. This classification is based on the observations in Japan where three fairly distinct forms were observed.

1. Very severe cases (exposure believed greater than 600 r). Nausea, vomiting, and malaise begin one to two hr after exposure and continue for days; prostration, severe leukopenia, intractable diarrhea, and early sustained fever are seen. Death may occur any time within fourteen days. Purpura and epilation may appear shortly before death.

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DISEASES OF THE EYE

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The purpose of this review of ophthalmic articles appearing in the literature between September 1950 and September 1951 is to present the salient features of original contributions which either facilitate the understanding of disease processes or bear on medical therapy. Overlapping efforts along similar lines are generally not noted Surgical aspects, embryology, highly specialized physiology, and esoteric subjects are excluded For convenience in classification the general field of ophthalmology is divided into thirteen sections, as indicated by the subtitles.

The past year has witnessed not only the usual progress in definition and and clarification of ocular disease entities but has produced several contributions which bear significantly on the processes of general disease. Retinal capillary microaneurysms, which for some years have been considered the earliest specific ocular evidence of diabetes mellitus, are now recognized in other general vascular diseases They have been produced by experimental occlusion of the central retinal vein and bid well to become one of the most common retinal lesions found by the careful ophthalmoscopist. There is some evidence that diabetic retinopathy, formerly felt to advance slowly and relentlessly in spite of general diabetic management, may be partially related to the thoroughness of such management, and may even be improved by attention to other hormone therapies. The current treatment of choice in ocular tuberculosis—streptomycin and para-aminosalicylic acid—has been rather well established on both experimental and clinical grounds Specialized investigation concerning facility of aqueous outflow seems to have eliminated the old speculative possibility of aqueous hyperformation in the etiology of glaucoma, and has done much to define the important role of drainage block mechanisms in practically all types of glaucoma.

Ophthalmic Aspects of Systemic Disease

Retinal vascular findings in forty confirmed cases of coarctation of the aorta have been studied by Granstrom (1). Twenty-four of these showed a characteristic, corkscrew tortuosity distinctly affecting the retinal arterioles but not the venules Usual signs of hypertensive retinopathy were quite inconspicuous; hemorrhages or exudates were found in none of these cases. Most of the patients were in the third decade of life (age range of 8 to 42

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mended on the basis of 52 operations reported Treatment with Vitamin E has not shown any significant effect on the process. On the basis that hyperadrenalism inhibits the growth of mesenchymal cells, and that cortisone specifically inhibits capillaries, therapy with corticotropin (ACTH) has been attempted in 14 infants Doses of 25 mg per day have been given for periods of two to four weeks in cases where the fundus signs show definite progression. Mere dilatation of retinal vessels is not an adequate indication for ACTH, because regression commonly occurs from this stage Results so far have been discouraging both for arrest and regression of the processs

Neurology and Visual Fields

Falls (5) reports on ophthalmic surveys conducted the day before, immediately after, and one day following iodopyracet (Diodrast) or colloidal thorium dioxide (Thorotrast) injections of the common carotid artery in 80 consecutive patients Petechial hemorrhages were seen in the conjunctiva in 80 per cent of cases Similar retinal hemorrhages occurred in 25 per cent, and these were frequently associated with cotton wool exudates or white centers in the hemorrhages Skin petechia appeared in 45 per cent, dilatation of the pupil in five patients for 3 to 24 hr., and severe optic neuritis and blindness in one case One death followed the injection and resulted from subsequent internal carotid artery thrombosis Ocular pain, temporary visual loss, and retinal arterial occlusion have also been reported following arteriography.

Both the definition and etiology of ophthalmoplegic migraine have long been the subject to some question, but cerebral aneurysms have been thought to play a causative role Alpers & Yaskin (6) report two typical cases in which carotid arteriography was done and no aneurysms could be demonstrated on satisfactory films One patient died 48 hours following the procedure and on autopsy was found to have thrombosis of the internal carotid artery. However, careful search confirmed the absence of aneurysms Five other autopsy reports collected from the literature also failed to show aneurysms in cases of ophthalmoplegic migraine Thus the cause continues unknown, but evidence at hand seems to exonerate cerebral aneurysms

In anatomic study of necropsy specimens by Walsh & Hedges (7) tortuous venous channels were noted emerging from the bone of the optic canal in cases of massive cerebral hemorrhage, a few similar channels were seen leaving the optic nerve. This suggests that optic nerve sheath hemorrhages do not originate by forward passage of blood from intracranial meningeal spaces, but rather by rupture of venous channels in the dura of the optic nerve In 90 cases of spontaneous intracranial, subarachnoid hemorrhage, associated optic nerve sheath hemorrhages were predominantly subdural. In many cases optic nerve sheath hemorrhages have been found without intracranial hemorrhages A marked correlation exists between the severity of a cerebrovascular accident (with its cerebral edema) and the extent of optic nerve sheath and retinal hemorrhages Increased venous pressure is

years) In common with generalized arterial tortuosity seen in the upper half of the body in coarctation, the retinal findings were more common in patients over 20 years of age. Careful ophthalmoscopy may differentiate this condition from juvenile hypertension.

In a survey of 100 cases of multiple sclerosis, Yaskin, Spaeth & Vernlund (2) found 56 to have ocular abnormalities at the time of hospitalization. Twenty-seven had ocular manifestations in the absence of other symptomatology at the onset. These patients had vague complaints of blurred vision, jumpiness of vision, difficulty in focusing, and gradual but progressive loss of vision. Among the 100 patients, 73 presented nonocular, subjective findings which facilitated the neurologic diagnosis. Nonocular signs and symptoms may not appear for months or years following the initial complaints. This places on the ophthalmologist a difficult task. he must exclude brain tumors, vascular disturbances, and similar conditions which can simulate multiple sclerosis, and at the same time he must not rush to the diagnosis of multiple sclerosis in each case of minor, unexplained visual complaint.

From the study of 12 cases of severe, malignant exophthalmos Falconer & Alexander (3) feel that separation of this process into thyrotopic and thyrotoxic is an oversimplification, and not justified by essentially identical orbital biopsies in six cases which showed edema, fibrosis, and inflammatory cell collections in either type. Similarly, blood thyrotropin levels in 11 cases failed to follow the thyrotropic-thyrotoxic pattern. They conclude that malignant exophthalmos is a self-limited condition, loosely associated with known thyroid mechanisms, usually unimproved by thyroidectomy and, in some cases, aggravated by medical or surgical thyroidectomy. In mild cases they withold treatment; in more severe cases they use tarsorrhaphy or, in later cases, orbital decompression In exophthalmic cases of moderate degree, bed rest or thyroid irradiation is probably safer than surgery.

Retrolental fibroplasia is considered in this section because of the preponderant element of neovascularization shown in the early, active phase and its common association with hemangiomatous tissue, particularly of the head region Reese & Blodi (4) point out that associated hemangiomas of the skin, choroidal plexus, carotid body, etc , tend to follow a development and recession course parallel to the activity of the retrolental process Histologic examination in 58 sets of eyes from premature infants who died shortly after birth revealed neovascularization in the vitreous of only one set hence it may be assumed that this condition is rare Uveal inflammatory changes were noted in 18 per cent of the eyes, which is about the same incidence as for retrolental fibroplasia in premature infants That such inflammatory changes may precede the neovascularization is suggested by vitreous floaters, pigmentary disturbances in the retina and synechia, which are commonly seen in active retrolental fibroplasia Surgical attempts to remove portions of the scar tissue between the lens and retina in older babies are not recom-

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the basic factor in these ocular hemorrhages and there is little, if any, extension of hemorrhage via the optic canal.

Bilateral medial rectus muscle paralysis on attempted conjugate lateral gaze, without other evidence of Nerve III paralysis, is known as internuclear ophthalmoplegia It usually develops suddenly, with associated vertigo, and generally is due to multiple sclerosis. The lesion is located in the medial longitudinal fasciculus Cogan and his co-workers (8) report a more rare paralysis of one medial rectus on attempted contralateral gaze, with the preservation of good convergence in eight additional cases. This is referred to as unilateral internuclear ophthalmoplegia. The course and onset are similar to the bilateral syndrome but the cause is usually vascular (infarction). One autopsy examination was obtained and revealed an infarct in the homolateral medial longitudinal fasciculus.

Continuing his series of earlier publications on the testing of visual fields by the flicker fusion phenomenon, Miles (9) reports 47 cases studied by both conventional perimetric techniques and the flicker method. He feels that the end point is more critical and more easily obtained by the flicker method In 28 of his 47 cases more satisfactory information seemed to be produced by his technique than by the older method. This procedure seems to be less time-consuming than is the use of ordinary test targets.

The Orbit and Exophthalmos

Eosinophilic granulomas of the orbit were first described by Lichtenstein & Jaffe (9a) in 1940, and have, in at least one case, been found to be limited to the orbit. Beller & Kornbleuth (10) report two other cases, one in a boy of 14 years and the other in a girl of 2½ years. Both are confirmed histologically. As in the other reports of this disease, the patients are usually in the first two decades of life; the tumor progresses rapidly over a period of several months, and blood counts and sternal punctures are usually normal, with the exception of a 4 or 5 per cent eosinophilia. Antecedent history of mild trauma is often obtained. Beller & Kornbleuth's tumors were removed piece-meal by transfrontal orbitotomy. Deep x-ray therapy to 2,000 r was administered postoperatively but no follow-up observation is reported. Another case report along similar lines has been added by Babel (11).

Mucormycosis is reported by Stone (12) in a 42-year-old negress with orbital cellulitis, intraocular tumor mass, and death from acute meningoencephalitis with cavernous sinus thrombosis. As in most cases of mucor, there was uncontrolled diabetes. A case manifesting unilateral retinal tumor in a 10-year-old boy without diabetes or systemic reaction has been enucleated by Wadsworth (13). This picture of ocular mucormycosis was considered as a possible Coats' disease or retinoblastoma. Treatment seems to be ineffectual.

Further investigative reports with the original orbital tonometer designed by Copper have been extended, and the tool promises to be useful

in differentiating retrobulbar, space-taking lesions In Cushing's disease Copper (14) reports that the total displacement of the globe appears normal, but the displacement curve appears flattened, indicating increased orbital tension. Offret (15) reports pessimistically on this instrument but feels that it deserves further study in relation to diagnosis of orbital neoplasm.

Therapy

As in almost every field of medicine, the use of ACTH and cortisone has continued to hold a central location on the stage of therapeutic investigation. Individual and collected series of cases have reached significant numbers in most of the more frequently encountered diseases where these agents might be of value. Olsen (16), Scheie (17), Mosher (18), Woods, (19) and many others (19a, 19b) have reported essentially agreeing clinical observations that the most conspicuous effect is noted in cases of acute anterior uveal inflammations. Only mild remissions are to be expected in chronic cases; those with degenerative elements and anatomical changes are not responsive. The most effective mode of treatment in acute anterior inflammations seems to be by frequent instillation of drops (5 to 25 mg./cc. and at 30- to 120-min. intervals depending on the severity) or ointment (10 to 15 mg /gm used less frequently than the drops) containing cortisone Seventy-five to 80 per cent of these cases generally respond rapidly, but remissions are to be expected as the administration of the drug is tapered off. Posterior segment inflammations respond somewhat to intramuscular cortisone or ACTH, but show no response to orbital injection or conjunctival instillations. Negative reports are accumulating in regard to Tay-Sachs disease, central serous retinosis, chronic granulomatous posterior uveitis, keratitis metaherpetica, Eale's disease, and rodent ulcer

From the physiologic point of view, Armstrong (20) points out that ACTH and cortisone (*a*) reduce the exudation of eosinophils, neutrophils, and round cells, (*b*) reduce the permeability of capillaries in inflammatory areas, and (*c*) reduce the proliferation of granulation tissue and the fibrotic reaction. When inflammatory reaction has a defensive function, however, these hormones can be deleterious, and if clinically unsuspected bacterial infections are present in organs other than those under consideration (e g., [illegible] d and fatal com-

[illegible] the war against trachoma still appear in the literature The weight of evidence, however, indicates that secondary invaders in trachomatous eyes are reduced by almost any of the antibiotics, while the essential process of trachoma remains unaltered [Shah (21), Poleff (22), Ching (23)] Sulfa drugs still seem to be the most effective agents against the trachoma virus

Continuing studies by Wood (24) on experimental ocular tuberculosis confirm the deterrent effect of para-aminosalicylic acid on this disease proc-

ess The combination of streptomycin with para-aminosalicylic acid seems more effective than either drug alone, and has essentially the same effect as streptomycin and thiozolsulfone (Promizole) but without the more toxic effects of the latter drug.

Grant (25) reports a follow-up analysis of 60 cases of primary glaucoma treated unsuccessfully by conventional miotics, and hence changed to tetraethylpyrophosphate (TEPP). Ten per cent developed local sensitivity to TEPP, and in 40 per cent the drug was discontinued because of ineffectiveness. In 16 cases di-isopropyl fluorophosphate (DFP) was found to be equally effective and the TEPP discontinued. Thus the drug seems to be comparable in effectiveness to other strong miotics, but it has no outstanding advantage and may induce sensitivity. In common with DFP it is decomposed by water.

Douvas, Featherstone & Braley (26), in a clinical study of terramycin in common external eye infections, found penicillin to be generally more effective than terramycin on gram-positive organisms. Chloramphenicol and streptomycin were apparently more effective than terramycin against gram-negative organisms cultured from common external inflammations. Terramycin showed no effect in four cases of herpes simplex and two cases of Beal's conjunctivitis.

Many data concerning optimal use of drugs, incompatibilities, and side reactions are collected in Leopold's review of pharmacology (27). Because of necessary and important host factors in the activity of aureomycin and chloramphenicol (unlike penicillin), clinical trial is urged as the method of choice in selecting antibiotics. Attempts at identification of pathogens, however, should proceed concurrently with the introduction of antibotic therapy. Effective dosage may be achieved theoretically by either continuous or interrupted medication, provided the intervals between administration are not long enough to allow a secure reflourishing of the pathogens. Low doses of some antibiotics may stimulate bacterial growth. Resistance to terramycin is common also to aureomycin and streptomycin. Advantageous combinations, as aureomycin and streptomycin against Brucella organisms, can be effected, but definite antagonistic effects also occur as between penicillin and chloramphenicol. The use of multiple agents should not be undertaken unless their combined behavior pattern is known Skin tests are generally unsatisfactory in predicting sensitivity to antibiotics. Gastric upsets associated with the oral administration of antibiotics can be lessened by the simultaneous ingestion of food, but the various aluminum, anti-acid gels should not be given because they interfere with the obtaining of good serum levels.

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increased output of 11,17-hydroxysteroids during foreign protein therapy, found eosinopenia in patients showing good response to foreign protein therapy. This effect was maximal about 18 hours after injection, and was

not seen in patients who responded poorly to foreign proteins It is postulated that at least part of the effect achieved by this well-tried method of therapy rests on the more recently understood mechanism of cortisone liberation.

The Iris, Ciliary Body, and Choroid

Harada's disease and the Vogt-Koyanagi syndrome are thoughtfully analyzed by Cowper (29) in the light of a reported case containing features of both diseases, He has found electro-encephalographic disturbances indicating a diffuse process at the same time that spinal fluid examinations showed increased cell counts and abnormal second zone colloidal gold curves He feels that differentiation between these two diseases is largely artificial and they both should be considered as uveo-encephalitis, probably of infectious nature and resulting from a yet unidentified virus agent All cases of these diseases should have virus identification studies on the spinal fluid and, if possible, similar studies on aspirated aqueous.

Malignant lymphoma is reported by Cooper & Riker (30) from histologic diagnosis of an enucleated eye and excised testicle in a 27-year-old white man treated for chronic, nonspecific uveitis The original impression was established because of mutton fat keratic precipitates, cells in the aqueous, thickened iris, retinal hemorrhages, retinal vein engorgement and periphlebitis, secondary glaucoma, and ciliary flush Extensive etiologic studies were negative, as were repeated blood counts The patient made no response to various types of therapy for uveitis and the eye was ultimately enucleated for pain. The patient died of generalized lymphomatosis in spite of massive x-ray treatment to lymph nodes over the entire body

The two distinct types of traumatic iris cysts are reviewed by Sitchevska & Payne (31). Pearl or implantation cysts are to be differentiated from serous or epithelial invasion cysts because the former are usually associated with the implantation of cilia in the anterior chamber. Treatment of choice has been surgical excision by iridectomy, but in some cases good results have been reported by electrocoagulation. The clinical course is divided into three phases (*a*) an asymptomatic period of several months; (*b*) the period of iridocyclitis and occasional sympathetic involvement; and (*c*) secondary glaucoma If left alone, the ultimate prognosis is loss of the eye A typical case is reported following an initial repair of a lacerated cornea and the removal of two cilia from the anterior chamber The debridement appeared complete but apparently the pearl cyst can develop from even a few epithelial cells left in place

Lacrimal Apparatus

The rose bengal test (1 per cent solution in normal saline or 1·5,000 benzalkonium chloride (Zephiran) has been studied in earlier foreign literature and is introduced to English language literature by Forster (32) in a study of 100 arthritic patients These individuals are known to be susceptible

to keratoconjunctivitis sicca, and diagnosis by the standard Schirmer test is felt to be unreliable in early degrees of deficient tear formation The rose bengal test is innocuous except for mild stinging and, in positive cases, a persistence of the rose staining for several hours. Excess dye is flushed out after conjunctival instillation of one drop of the solution, and the intensity with which the conjunctiva or cornea stains may be roughly graded Comparison of the Schirmer test and the rose bengal test in this series showed good correlation only in advanced cases of tear deficiency. No positive Schirmer tests occurred in the presence of negative rose bengal tests, and twenty mildly symptomatic cases which had positive rose bengal tests showed negative Schirmer tests These latter cases were relieved by the use of artificial tears. The test appears to be simple and of considerable value in the early diagnosis of keratoconjunctivitis sicca.

Furtrethonium iodide (Furmethide iodide) has been used sporadically in the last five years by Shaffer & Ridgway (33) in 21 glaucoma patients, each of whom received the drug for periods of three months or longer. Seventy per cent of these individuals developed chronic tearing and some degree of lacrimal obstruction. In most cases there was permanent obstruction because of granulation tissue and fibrosis. Similar nonspecific inflammatory changes (without eosinophils) were seen in conjunctival biopsies. The authors feel that this is a drug reaction, thus limiting the usefulness of furtrethonium iodide to short courses of treatment only. Tearing is an indication for immediate discontinuance of the drug.

The Retina

Two functionally parallel studies, each reporting a series of about 100 cases of central retinal vein thrombosis, afford an unusual opportunity to evaluate therapy in this condition Anticoagulants were used by Larson & Nord (34) but not by Braendstrup (35). The final visual acuities and the incidence of hemorrhagic glaucoma were essentially the same in the two series Thus the treatment by anticoagulants continues to be of theoretical interest but of little demonstrable practical value.

Post & Stickler (36) review 59 patients who were known diabetics prior to the age of 15 years and regularly followed by the Departments of Medicine and Pediatrics at Washington University. Fifty-four per cent showed retinopathy, and only two patients with diabetes for as long as 15 years had normal fundi The amount of retinopathy was closely related to the degree of renal impairment, and also to the adequacy of the control of the diabetes This latter fact mitigates to some degree the feeling of inevitability sometimes held in regard to the development and progression of diabetic retinopathy even in apparently controlled cases. The recent study by Joslin (36a) also emphasizes that strict treatment of diabetes pays. Of associated interest is the figure of 20 per cent retinopathy in 160 juvenile diabetics reported from Berlin by Kumm (37); he attributes this high incidence (actually less

than one-half that reported by Post and Stickler) to adverse conditions and poor insulin supply in Berlin in the last few years.

Another encouraging attack on diabetic retinopathy has been made by Saskin, Waldman & Pelner (38) based on frequent liver insufficiency in diabetics. In the presence of such liver disorder, androgens appear to be inactivated as usual, but estrogens are not. Thus a relative excess of estrogens is created. This is correlated with the more common incidence of diabetic retinopathy in females than in males, though diabetes mellitus occurs with about equal incidence in the two sexes. Similarly, retinopathy appears in the presence of diabetes of shorter duration in the female than in the male. By the use of testosterone propionate (methyl testosterone is contraindicated) in doses of 25 and 50 mg. intramuscularly, alternating weekly, the authors report unequivocal improvement in retinal hemorrhages in more than one-third of 28 cases studied No change was noted in retinitis proliferans or arteriosclerotic findings

Sorsby (39) has studied 24 individuals from three generations of the same family and found allied retinal pathology in eight. Seven of these showed various types of detachments and the eighth showed retinal scarring compatible with previous detachment The presence in some of these cases of cystic degeneration of the retina, falciform folds, congenital vascular veils in the vitreous, total congenital detachment, and extensive retinal atrophy, plus the fact that each of these conditions generally has been thought to be sex-linked recessive, suggest to Sorsby that all of these conditions are stages of one pathologic process, i e , cystic degeneration of the retina If borne out by further family pedigree studies, this suggests more strongly the unpleasant prognosis to be given in cystic degeneration of the retina

Retinal microaneurysms in eyes removed from nondiabetic cadavers at routine port-mortem and surgically recovered globes from nondiabetics were studied by Ashton (40) using the McManus periodic acid-Schiff technique stains About one-third of the eyes studied showed these microaneurysms, generally on the arteriolar side of the capillary bed, and usually in the extreme retinal periphery. Apart from vascular sclerosis, these microaneurysms are felt to be the most common retinal lesion, and no longer can they be considered as the earliest positive ocular sign of diabetes. Similar studies were made on post-mortem eyes of 40 patients who died of hypertensive vascular disease (41), and numerous capillary aneurysms were seen in each case of malignant nephrosclerosis, but in only 1 of 29 patients who had nonmalignant hypertension. These aneurysms differ slightly from those seen in diabetes as the latter occur at the venous end of the capillary bed.

Glaucoma

In a fundamentally significant study on glaucoma mechanisms Grant (42) reports 1,000 measurements on 600 eyes, according to the recording tonographic technique previously described by him. In this procedure an

electronic Schiotz tonometer is placed on the topically anesthetized cornea for a period of about 5 min., while a continuous record of the fluctuations is made on moving paper by a galvanometer apparatus similar to that used in electrocardiographs The values obtained are converted to actual intraocular pressure, increment of intraocular pressure resulting from weight of the tonometer, and changes in ocular volume, all according to the "absolute" calibration data evolved by Friedenwald in the last year. Predicated on the steady state of aqueous formation and outflow, these data then enable the calculation of aqueous ouflow and aqueous formation in cu. mm. per min A normal of 0.22 c. mm. per min. (range, 0.11 to 0 44) has been established All glaucomatous eyes have consistently shown poorer facility of aqueous outflow, which is generally proportional to the elevation of tension and the presence of embarrassing factors in the drainage mechanisms In periods of compensation achieved by remission, miotics, or surgery, the facility of outflow is seen to increase. Secondary glaucoma, including glaucoma capsulare, has shown similar decreased facility of outflow. For the first time it has been demonstrated clinically and mathematically that increased formation of aqueous is not a true problem in any type of glacuoma seen clinically.

Though this review is concerned only with medical ophthalmology, it is important to note Berens' report (43) on 65 glaucomatous eyes treated by the simple and apparently effective procedure of cycloelectrolysis. This may well become an office procedure for most types of glaucoma which do not respond to medical therapy. Cycloelectrolysis is essentially a chemical attack on the secretory activity of the ciliary body by galvanic current which produces no thermal or sparking effect Five m amp. at 22 5 v. are used The positive or dispersive pole is placed beneath the patient's shoulders and the negative or active pole is connected to a platinum needle, 2.0 mm. long and 0.18 mm. in diameter. With this apparatus two arcs of transconjunctival punctures are made, 1 and 3 mm. from the surgical limbus; 50 to 75 punctures lasting 5 sec. each are made and usually confined to one-half of the globe. If intraocular pressure remains elevated immediately after electrolysis, a paracentesis may be done; atropine is instilled. Transient iridocyclitis has occasionally followed the procedure. The only contraindications at present seem to be intraocular tumor, glaucoma capsulare, and dislocated lens.

The Conjunctiva

Many reports concerning substitution of antibiotics or merely saline flushes for the well-established Crede prophylaxis of ophthalmia neonatorum have appeared during the past year. Compared to earlier reports of untreated newborns, all of these procedures seem to be of value and must be evaluated carefully in regard to sensitization Improved pre-natal care has certainly done much to reduce the incidence of this disease. Culler & Clark (44) in a continuation report have now followed nearly 3,000 live births in which

aureomycin prophylaxis (one drop of the 0.5 per cent borate solution) was used. Their incidence of opthalmia was 1.2 per cent and this included one case of gonorrheal ophthalmia and one case of inclusion blenorrhea. Thygeson in 1936 found a 6 6 per cent incidence of infected eyes in approximately 4,000 newborns receiving Crede prophylaxis

The spreading use of BCG vaccination in tuberculin nonreacting children in Europe is stimulating interest in possible tubercular eye complications following such vaccinations. From Malta, Damato (45) reports that in several children limbal phlyctenules developed two to six weeks after intradermal BCG vaccination He feels that this strengthens the tuberculo-protein allergy-anaphylactic etiology of phlyctenular disease and cites the low incidence of this process associated with the recent BCG program in Malta. A similar and somewhat insecure attempt to link three cases of chronic posterior uveitis with BCG vaccination is made by Frandsen (46) on the basis of lesions which developed in children of 15 to 18 years of age, 2 to 18 months after vaccination

Phlyctenular keratoconjunctivitis in 26 cases, largely from Alaska, has been treated with topical cortisone by Thygeson & Fritz (47). They noted dramatic relief usually in 24 to 48 hr, with occasional flare-ups when the medication was discontinued. Cortisone acetate, 12.5 mg./cc, was instilled hourly in initial therapy, and in some cases reduced dosage was continued for several weeks

Newcastle virus disease, which has become a widespread poultry infection in America, has been transmitted to humans, and a case is reported by Keeney & Hunter (48) with recovery of the virus from the conjunctiva and the blood stream In humans the disease is manifested by a granular conjunctivitis, usually unilateral and associated with preauricular adenopathy of several days' duration. Mild systemic complaints such as malaise, muscular aches, headaches, and fever may occur transiently. Serum antibody response can be demonstrated (49). The disease is apparently benign, self-limited, and requires only symptomatic care for the photophobia and discomfort.

The Cornea and Sclera

Swan (50) has rather thoroughly re-evaluated scleral disease Clinically and histologically scleritis is divided into suppurative (primary or secondary) and granulomatous Both types are usually found anteriorly around vessels and associated with secondary uveitis The presence or absence of nodules was not considered etiologically significant by Swan Secondary glaucoma is a common sequela of granulomatous scleritis, especially if annular in distribution Consequently mydriatics should not be used for extended periods of time without gonioscopic check-ups. Although syphilis, tuberculosis and sarcoid are considered as classically causative factors, acute upper respiratory infections, or direct chemical irritation (as by subconjunctival injection of atropine or mercury) may lead to granulomatous scleritis The diffuse

collagen diseases may affect the sclera either in association with other lesions or as single focal manifestations. It is in these cases that ACTH and cortisone seem to be of value. The less common fibroblastic ingrowths into the eye should be differentiated from their more destructive cousins, epithelial ingrowths Such fibroblastic growths generally come from the episclera and characteristically grow on the surface of the vitreous, clinging to the cornea only where the endothelium has been damaged. The lesions have a woven cloth-like texture, with edges which appear frayed. These processes are usually self-limited, or can be cured with small doses of radiation. The epithelial ingrowth, on the other hand, is much more destructive and is resistant to therapy. In older patients, particularly those with osteoarthritis, hyaline plaques in the sclera without associated inflammatory changes are common findings, and offer no complication to cataract extractions other than slightly slower wound healing.

Johnson & Nosik (51) describe two cases of superficial petrosal neurectomy for relief of chronic bullous keratitis. This approach reduces the lacrimal secretions, thus dehydrating the epithelial vesicles. The surgical approach is similar to that for the sensory root of the trigeminal nerve, and almost immediate postoperative reduction in lacrimation and pain was reported by the two patients.

The search for a less painful and equally effective treatment for herpes simplex has been continued, as reported in many publications this year. Hallett & Leopold (52) found that in experimental animals cortisone intensifies the reaction, and none of the currently available antibiotics was of clinically significant value Combinations of antibiotics were of even less value than when used singly.

Pyocyaneous infections of the cornea are generally of tragic visual result and often precipitated by only minor trauma. In 10 reported cases Bignell (53) emphasizes early clinical recognition of the dense white ulcerations with hypopyon in order to attain any response to therapy. His regimen consists of hourly conjunctival instillations of streptomycin and daily subconjunctival injections of 0.5 gm. streptomycin Treatment should be continued for several days, despite angry appearance of the conjunctiva, after the ulcer appears to have healed.

The Lens and Cataract

Further investigations of the physiology of the lens have been reported by Kinsey & Merriam (54) indicating that the lens proteins are not inactive but participate in lens metabolism. The actual metabolic disturbance producing opacification of the lens has not yet been identified, but significant inroads are being made in this field

The action of microwaves of 3 to 10 cm length (including the "radar" type of wave) has been investigated in animal eyes (55, 56) and appears to produce sutural cataracts and slowly progressive anterior cortical cata-

racts, possibly by thermal elevations within the lens. Significant clinical cases have not been clearly documented, but individuals exposed to these microwaves for long periods of time should have periodic ophthalmic examinations.

Interest in radiation cataract has been rekindled by the occurrence of cataracts in cyclotron workers (61) and in some persons exposed to radiation from atomic bomb (62) Cogan & Donaldson (63) have reviewed this subject and reaffirmed the susceptibility of the youngsters to irradiation Granules, vacuoles in the lens, and cellular change in the lens epithelium were among the earliest changes. They employed x-rays of 200 and 1,200 kv. energy in doses of 250 to 3,000 r and rabbits ranging from 3 weeks to 3 years

Experiments by von Sallmann & Locke (64) did not lend support to the theory that enhanced permeability of the lens or depressed processes of phosphorylation lead to the development of lenticular opacities produced by roentgen rays but suggested rather that these changes accompany and possibly influence the progress of the opacification. Krause & Bond (65) have also reviewed the subject of neutron cataracts and concluded that neutrons produce more damage per unit of absorbed energy than roentgen rays

Industrial

Chemical burns continue to be a major industrial source of visual loss and the therapy of such burns is often unsatisfactory. In an attempt to re-evaluate the role of paracentesis following alkaline burns Grant (57) conducted animal experiments which showed no significant effect in any case. The actual mechanism of anterior segment damage in alkaline burns of the cornea remains obscure and seems unrelated to transient elevations of the aqueous pH or the presence of ammonia ions per se, because these are only of mild degree in the presence of severe burns The best treatment for chemical caustics still appears to be early, copious irrigation with water.

Miscellaneous

Visual illusions in night flying have been extensively studied by both clinical and laboratory means by Imus (58) over a period of several years Experienced aviators report consistent illusions which appear to be unaffected by experience and can be reproduced in the human centrifuge or Link trainer Apparent displacement, post-rotational movement and oculogravic illusions resulting from acceleration occur commonly and are most intense in darkness or bad weather For example pilots are generally unable to tell whether they are in a climbing turn or diving turn when flying in dense fog or at night Fear of these illusions is reduced by helping pilots to understand them, by the presence of more formation lights on the aircraft, and by having the pilots place reliance on their instruments

Brunner and Bieberdorf (59) report on injury to the eye by mesquite thorns, which are one of the most common forms of vegetation in south-

western America. Infection is common, and the thorns are often contaminated by *Alternaria* Certoic acid content of the thorns is very irritating to eyes, and such thorn wounds heal poorly. In cases of injury with this agent, prompt and complete removal with usual treatment for iritis is urged. Systemic iodides are useful if *Alternaria* contamination is associated.

The causative agent in sympathetic ophthalmia is postulated by Schreck (60) to be of rickettsial nature. This author has added apparent experimental verification to his previous publications on this thesis. He reports the cultivation of rickettsia from involved eyes by use of chick embryo inoculations. His previous reports on anatomical specimens suggested a spreading perineuritis and perivasculitis from the exciting eye, via the optic chiasm, to the other eye He suggests that diagnosis in clinically questionable cases may be verified by diagnostic puncture and aspiration of the anterior chamber. On this basis treatment with *p*-aminosalicylic acid, *p*-aminobenzoic acid, and aureomycin is suggested.

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY[1]

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INTRODUCTION

Immunohematology has been chosen as the theme for this chapter on "Laboratory Aids to Diagnosis and Therapy." The idea that immunologic phenomena have a part in hematologic disorders is almost half a century old, but recent technical developments have transformed this branch of hematology into a separate and distinct discipline with its own methodology. The name expresses aptly the enrichment of hematology by application of immunologic techniques to the solution of its unsolved problems.

New names in medicine are attractive and unless clearly defined invite application to conditions which do not belong to them. Therefore, it may not be amiss to suggest a definition of the term "immunohematology" and in this way forestall unecessary confusion. I had to attempt to define the scope of immunohematology for my own use in order to delimit the subject assigned for this chapter. Immunohematology encompasses diseases of blood of which the cause, the pathogenesis, or clinical manifestations have been shown to be determined by an antigen-antibody reaction The various hemolytic anemias, fetal erythroblastosis (hemolytic disease of the newborn), and infectious mononucleosis obviously belong here Blood group factors are included in so far as they are responsible for hemolytic transfusion reactions and fetal erythroblastosis. Acute disseminated lupus erythematosus (LE) is not a disease of the blood, but the so-called LE phenomenon should be treated here inasmuch as its immunologic character has been disclosed recently It may well be that further progress will add other diseases to those mentioned, if antigen-antibody reactions are shown to be involved in them. For example, there are indications that thrombocytopenic purpura, or at least some forms of this disorder, may have to be included.

HEMOLYTIC ANEMIAS

The advances in the study of Rh antibodies, especially the discovery of new techniques for detection of incomplete antibodies, have been applied to hemolytic anemias with highly beneficial results The responsibility of antibodies for hemolytic manifestations in some forms of anemia has long been established, but the demonstration of such antibodies was a haphazard affair. Though reported by some writers, it could not be duplicated by others The reason has become apparent only recently The antibodies in-

[1] The survey of the literature pertaining to this review was concluded in September, 1951.

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forms most of the antibody during the first phase of immunization. After a single dose of antigen (sheep red cells), the spleen apparently forms a relatively large quantity of antibody within a short period, whereas the rest of the antibody forming sites maintain a low antibody level over a long period [Taliaferro *et al.* (6)]. Splenectomy depressed antibody formation (to about 20 per cent on the average) in the majority of rabbits when it was done on the day of immunization or through the fourth day. There was no noticeable effect of splenectomy when it was done on the sixth and eighth days. Contrasted with the rapid increase of the antibody in the early phases of immunization, nonsplenic sources form antibody at a rate only slightly less than the rate of antibody decay over a long period, and probably produce more total antibody than the spleen. Also, in the fowl the spleen seems to be an important site of antibody formation. Splenectomy reduced the ability of chickens to produce precipitin [Wolfe *et al.* (7)]. This lowered production could be overcome to a limited extent by increasing the dosage of the antigen. Splenectomy decreased antibody formation but did not eliminate it completely, indicating that this function is also carried out in other organs.

A different function of the spleen was demonstrated by Jacobson and associates (8) Severe anemia, leukopenia, thrombocytopenia, and reticulocytopenia developed in mice exposed to 1,025 r whole body x-radiation without lead protection of the spleen. No animal thus exposed survived beyond the thirteenth day after irradiation. On the other hand, no significant anemia and only transient leukopenia and thrombocytopenia developed with the same dosage when the spleen was lead protected Forty-two per cent of these mice survived beyond the twenty-eighth day of observation. Lymphatic tissues (thymus, lymph nodes, and spleen) of mice without lead protection of the spleen during irradiation were reduced to a reticulum stroma, and no recovery was apparent during the 13 days of observation Hematopoiesis in the bone marrow was destroyed. With lead protection of the spleen, the lymphatic tissues were never completely depleted of free cells and resumed an essentially normal cellularity by the seventh day after irradiation. The marrow was never depleted of free hematopoietic cells and was normal in cellularity at seven days These findings suggest a humoral control by the spleen over hematopoiesis

Splenectomy did not change the course of events in rats injected with a rabbit immune serum against rat erythrocytes. The amount of antiserum required and the changes in the peripheral blood and marrow were identical in normal and splenectomized animals [Tischendorf *et al.* (9)].

Adrenocorticotropic hormone (ACTH) —Reports on the behavior of antibodies in hemolytic anemia treated with ACTH differ. In some cases, the previously positive Coombs test became negative (4), in some, the titer of the Coombs test dropped (10); in others again, the titer of the Coombs test was not affected by the therapy, although the clinical manifestations of the hemolytic anemia were improved to a varying degree (11, 12) The irregularity of the antibody response to ACTH is in keeping with the fact that in

volved in the immunologic mechanism of hemolytic anemias are of the so-called "incomplete" variety; that is, they combine with the corresponding antigen but do not cause a manifest reaction unless special conditions are provided. They require one or more of the following: (a) special menstruum (human serum or albumin, bovine albumin) for dilution of the antibody containing serum and for suspension of the test red blood cells; (b) special techniques, for example, the use of antiglobulin immune serums (Coombs test); and (c) red blood cells made more susceptible to the antibody by pretreatment with enzymes. Application of the new techniques made the tests for antibody detection and for diagnosis of hemolytic anemia reliable and reproducible laboratory procedures. Most of the recent publications on hemolytic anemia have dealt with antibody tests, their application and interpretation. A recent article by Young and associates can be recommended as one of the introductions to the subject (1).

Congenital and acquired hemolytic anemia.—Until a few years ago, autoantibodies were supposed to be present in acquired hemolytic anemia and absent in congenital, and this distinction had served as a means of differential diagnosis. Recently autoantibodies have been seen also in cases of true hereditary spherocytosis, for example, in 32 per cent of a recent series [Wright et al (2)]. Some of these cases were in acute hemolytic crisis, but this condition is not an essential prerequisite for positive antibody tests. The test was positive in 48 of 58 cases of acquired hemolytic anemia, in six of nine cases of Cooley's anemia, and in three cases of multiple myeloma. There was no relationship between the presence or titer of antibodies and the activity of the hemolytic process, and no consistent response of titer to splenectomy

The importance attached to the role of antibodies in hemolytic anemias is best expressed by the recommendation to introduce the term "chronic hemolytic disease with erythrocyte-bound antibody" (1), and to assign to the antibodies an increasingly important place in the classification of anemias (3).

Among the questions that remain to be settled is the one regarding the relation between the various forms of antibody observed in hemolytic anemia. Is there any special significance to so-called autoagglutinins, autohemolysins, and antibodies reacting in the antiglobulin test (Coombs test), or do they all mean the same? Occasionally, the Coombs test is difficult to [illegible] ...tohemolysins

[illegible] ...h

[illegible] ...d

in the production of autoantibodies This conclusion is supported by the study of blood obtained from the splenic artery, splenic vein, and again from the splenic vein after injection of epinephrine into the artery, and after manual compression of the spleen (2). These observations suggest that the spleen is the initiating source of the autosensitizing antibodies Observations in intact and splenectomized rabbits indicate that the spleen ordinarily

ing because it is supposed to be the first case with a positive Coombs test, thus showing the presence of an antibody which is found frequently in cases of acquired hemolytic anemia. A positive Coombs test was also noted in a case of acute hemolytic anemia complicating infectious mononucleosis (20). Cases of acute hemolytic anemia in infectious mononucleosis (21) and in epidemic hepatitis (22) have been reported.

The improved methods of testing for antibodies may throw some light on the pathogenesis and nature of anemia in leukemia So far, the literature shows relatively few reports in which this problem has been critically investigated (23). Jonsson (24) reports a negative Coombs test in a patient with hemolytic anemia complicating chronic granulocytic leukemia, but the test was not done until after splenectomy.

Hemolytic crisis.—The pathogenesis of hemolytic crisis is the subject of two recent reports In one, the crisis was observed in four members of one family, all manifesting the characteristic features of congenital spherocytosis The Coombs test was negative in all (25). The crisis was attributed to hypersplenism and the spherocytosis to a congenital abnormality which has nothing to do with the activity of hemolysins. On the other hand, Li and associates (26) conclude from a study of a family of five, all with hemolytic crisis *occurring at about the same time, that hypersplenism* as well as Owren's acute marrow aplasia play a part. More studies on antibodies prior, during, and after the crisis may throw some light on the genesis of this complication.

The same statement holds for a variety of other atypical hemolytic anemias, which at the present are difficult to classify further than as atypical hemolytic anemia (27) Here belongs a case of "aplastic" crisis, seen during the course of a clinically demonstrable virus pneumonia in a patient with sickle cell anemia (28); also, another case of a hemolytic anemia with a negative Coombs test which was classified by Singer and associates as a thrombotic thrombocytopenic purpura (29), a case of a congenital, familial, chronic hemolytic anemia with ovalocytosis, without autoantibodies and a negative Coombs test [Kaplan & Zuelzer (30)], finally, two cases with abnormal susceptibility of red blood cells to hemolysis after chilling and acidification of the serum [Liu (31)] The patient's own serum as well as control serums were active. There was increased iron excretion in the urine, but no evidence of nocturnal intensification of the hemolysis In one of the cases, the Coombs test was negative A negative Coombs test was also described in a case of hemolytic anemia, methemoglobinemia, and false hemoglobinemia (32)

Crosby (33) described a hereditary hemolytic anemia occurring in members of a family in whom the anemia was associated but not genetically linked with brachyphalangia. All anemic members were of blood group A. Splenectomy had no noticeable effect This entity is set apart from hereditary spherocytosis

The Coombs test was negative in a case of paroxysmal nocturnal hemoglobinuria with chronic hemolytic anemia (34) Crosby (35) recommends a

general there is no consistent relationship between the titer of the antibodies and the severity of the hemolytic process. In some cases, the warm autoagglutinins disappeared completely and the cold agglutinins decreased in spite of the unchanged titer of the Coombs test (12). The osmotic fragility of the red cells may return to normal, and in at least one patient the ability of the serum to agglutinate normal red cells at an acid pH disappeared during the therapy (10). In Unger's case (11), there was no significant drop in antibody titer although the intensity of the clumping reaction was definitely diminished. Dameshek *et al* (12) explained the favorable effect of ACTH on hemolysis by the disruption of agglutinin production, presumably as the result of regression of lymphoid tissue in which the agglutinins are supposed to originate. The effect of ACTH on the pH may be responsible. According to Gardner (10), an acid pH may lead to sequestration and destruction of red cells in the spleen.

Origin of autoantibodies.—Wiener (13) suggests that the formation of autoantibodies in acquired hemolytic anemia is the expression of a particular readiness of the patient to produce antibodies.

Cold agglutinins.—The relation of cold agglutinins to autoagglutinins was studied by Bouroncle and co-workers (14) Depending upon the technique used, the titer of the cold agglutinins ranged from 1:2 to 1:64 in normal controls. It was within normal range in hereditary spherocytosis and was increased in some cases of idiopathic, acquired hemolytic ahemia There was no evidence of parallelism between cold agglutinins and incomplete agglutinins of hemolytic anemia. High titers of cold agglutinins were frequently accompanied by clinical hemolysis

Dacie (15) observed an interesting phenomenon of hemolysis in serum of seven patients with cold hemagglutinins of high titer The hemagglutinins acted best below room temperature, and not at 37°C The activity was affected by pH, being most pronounced in acidified serum. Red cells from patients with nocturnal hemoglobinuria were much more sensitive than those from normal persons Similar cold hemolysins were found in low titers also in normal persons, but they reacted only with red cells of patients with nocturnal hemoglobinuria. The author suggests that such hemolysins may be responsible for episodes of hemolysis seen in some patients

The association of cold hemagglutinins with acute hemolytic anemia, which was reported repeatedly in recent years, has again been emphasized in a case report in which the titer rose from 1:32 to 1:4,096 A false positive Donath-Landsteiner test was seen in this case (16). The authors recommend that in patients with primary atypical pneumonia chilling should be avoided, including the use of cold oxygen tents, sponging, and cold drinks They recommend administration of warmed blood when transfusion is needed. (It has been the reviewer's experience that blood must not be exposed to temperature higher than 37°C, even for the shortest period)

Cases of acute hemolytic anemia in so-called virus or atypical pneumonia have been described (17, 18) The report of Corelli & Ruggieri (19) is interest-

span when transfused into normal individuals. Normal cells transfused into patients with any of these diseases except acquired hemolytic anemia showed normal survival times. Patients with hereditary spherocytosis before and after splenectomy showed accelerated destruction of red cells before splenectomy and normal destruction after. In patients with acquired hemolytic anemia, the postsplenectomy survival of normal, transfused red blood cells was longer than before splenectomy. Normal red cells transfused into patients with hereditary leptocytosis survived normally. Blood of persons with the carrier stage of the anemia survived normally in the circulation of normal recipients From this fact, Kaplan & Zuelzer (40) drew the conclusion that there is a hemolytic component in hereditary leptocytosis. Brown *et al* (41) employed the same procedure in the study of leukemia Normal erythrocytes injected into patients with lymphatic leukemia showed a shortened survival time. The graph showed a curvature, which suggested that in leukemia there is not only an increased rate but also an abnormal method of hemolysis Normal erythrocytes injected into patients with acquired hemolytic anemia showed a shorter survival rate (42).

Radiation effect.—Schwab *et al.* (43) studied the well-known depressing effect of x-radiation on antibody formation in rabbits injected with bovine proteins Formation of precipitins was inhibited. The treatment also prevented formation of tissue lesions (glomerular and cardiac) following injection of a single large dose of bovine serum γ-globulin, as was seen regularly in control animals. In dogs exposed to total body radiation in single doses of 150 to 250 r. Davis *et al* (44) observed significantly increased bilirubin excretion during the first or second week after exposure but no changes in the morphology of the red cells or in the osmotic and mechanical fragility.

Red cell morphology—Mallarme (45) discusses the significance and specificity of morphologic changes of erythrocytes. None of them are absolutely specific for the congenital diseases they characterize Several of them may be combined in certain forms of anemia, leading to difficulties in classification. All morphologic deviations from the normal, though different in appearance and probably different in significance, have certain characteristics in common· they develop after the cells have emerged from the marrow into the peripheral blood and have passed the reticulocyte stage The deformed red cell (spherocyte, sickle cell, elliptocyte, or target cell) is, therefore, at the end of its cycle and its life is bound to be short. Erythropoiesis in the marrow is not involved This fact differentiates so-called erythrocytic dystrophies from megalocytic, because the latter result from an abnormality of erythropoiesis in the marrow

Chemically produced hemolytic anemia—Suppositories containing phenylsemicarbazide were responsible for six cases of acute hemolytic anemia in infants (46, 47) The drug was considered directly responsible for the hemolysis. Naphtalene moth balls have also been found responsible for acute hemolytic anemia (48) Traina showed that ascorbic acid in a dilution of 25 per cent was hemolytic for normal human erythrocytes at 4°C. (49), but not

new diagnostic test for this disease, the principle of which is activation of a hemolytic factor in normal serum by addition of thrombin. The test is simple and is supposed to be specific and to supersede some previously recommended procedures for making a specific diagnosis. In over 100 patients with paroxysmal nocturnal hemoglobinuria, the test was invariably positive. The author claims that the test is specific.

Schneider & Levin (36) demonstrated autoagglutinins in 13 patients with sickle cell anemia. They were also present in 4 of 11 cases with sickle cell trait, and doubtful agglutination was seen in two cases. A specific antiserum was produced in rabbits injected with red cells from patients with the disease. The antiserum agglutinated red cells of 19 patients with sickle cell anemia, but not those of 21 persons with sickle cell trait, or of 124 normal individuals The serum is recommended for differential diagnosis between sickle cell anemia and sickle cell trait.

Thrombocytopenia.—Wright *et al.* (2) have observed incomplete antibodies with the Coombs test and with enzyme-treated red cells in 6 of 21 cases of essential thrombocytopenic purpura, without any evidence of a hemolytic process in any of them. A similar finding in six cases of thrombocytopenic purpura without anemia, in four cases of thrombocytopenic purpura and acquired hemolytic anemia, and in four cases of acquired hemolytic anemia and thrombocytopenia without purpura, forms the background of a hypothesis put forth by Evans and associates suggesting that there is a spectrum-like relationship between acquired hemolytic anemia and primary thrombocytopenic purpura (37). More than half of the patients with primary thrombocytopenic purpura showed active hemolytic anemia This hypothesis is supported by the demonstration many years ago that injection of an antithrombocyte serum into an animal produces a picture which closely simulates primary thrombocytopenic purpura in man The authors recommend discarding the terms "hypersplenism" and "splenic panhematopenia" because the spl

"immunohemol

pancytopenia"

Survival of red cells.—Various techniques have been employed for the study of survival of red cells (38). The techniques make it possible to determine the part played by cellular defects, congenital or acquired, and extracellular mechanisms The shape of the curve on which the survival of the red cells is plotted tells the story. A rectilinear survival curve means that each cell has the same life span. When the life span is shortened and the disappearance curve is rectilinear, the implication is that a cellular defect has uniformly shortened the survival On the other hand, an exponential survival curve results when an extracellular destructive force removes the erythrocytes from the circulation at random, irrespective of their age

According to Wright *et al.* (39), red cells from acquired hemolytic anemia, hereditary spherocytosis, hereditary leptocytosis, paroxysmal hemoglobinuria, sickle cell anemia, and megaloblastic anemia had a shortened life

turned to positivity a variable number of days later. The titer of the direct Coombs test varied when checked over a period of several months, decreasing with warm weather (56). A false positive Donath-Lansteiner test could be produced by applying cold locally and producing stasis in extremities of healthy people. Intravascular hemolysis was observed [Stich & Korinth (57)]

THE Rh FACTOR

Most papers in this field during the last year or two have dealt with Rh antibodies.

Technique.—The so-called Chown capillary tube technique was subjected to a reinvestigation, in view of the criticisms expressed by various writers [Poole & Williams (58)]. In a total of 900 specimens, 2 per cent were found false, evenly divided among false positives and false negatives. Rouleaux formation and delay in the reaction were found responsible for the false results The test tube technique is still the most reliable. Dextran can be used as a substitute for albumin diluent in testing for Rh antibodies [Richardson-Jones (59)]. Speiser recommends porcelain plates with excavations for tests for the Rh factor and antibodies (60). As described, the technique can be used only for naked-eye examination.

Antiglobulin test.—The so-called antiglobulin test is constantly gaining in popularity as a sensitive and specific method for detection of antibodies. It is known popularly as the Coombs test, named after the author, who published it together with Mourant & Race as "a new test" in 1945 (61). Actually, if any name be attached to this test, it should be the name of Moreschi, who published the technique in great detail and with realization of its applicability as early as 1908 (62).

Rosenfield and associates described in detail the preparation and standardization of the reagents, especially of the antiglobulin serum, the technique of the test, the interpretation of results, the sources of error, and the application of the antiglobulin test (63).

The antiglobulin test is not only a very sensitive method of demonstrating Rh antibodies, but it was proved to be the only means of detecting some of the newer blood factors (for example, Duffy). It detects autoantibodies in hemolytic anemia The preparation of the antiglobulin serum and its standardization are complex procedures. Van Loghem presented his experiences and emphasized the role of the prozone phenomenon as the cause of false negative tests (64) Sources of error of this test are further analyzed by Hubinont & Massart-Guiot (65) They emphasize that there is no correlation between the results of the antiglobulin test and the intensity of iso-immunization. This conclusion is in contrast to the direct relation between the two phenomena in the serum albumin test. This technique employs human serum or bovine albumin as diluents, best by using AB serum as a diluent for the serum and 30 per cent bovine albumin for the suspension of the red cells

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at 37°C. At the latter temperature, ascorbic acid seemed to increase the resistance of red cells. The occurrence of hemolysis only at low temperatures may throw some light on the pathogenesis of some cases of cold hemoglobinemia. On the other hand, normal washed red cells were protected from hemolysis by 10 per cent solution of vitamin C when incubated for 1, 12, and 24 hr. (50). Ascorbic acid at concentrations of about 0.16 per cent of the hemolytic system was effective in protecting normal red cells from hemolysis This fact suggests to the author the possibility that ascorbic acid may be of therapeutic value in patients with increased fragility of red cells.

Pathogenesis of hemolytic anemia.—Evans *et al.* considered an endogenous toxic substance responsible for hemolytic anemia combined with methemoglobinema and false hemoglobinemia in two cases (32). In one of the cases, a bacterial infectious focus liberating nitrates into the blood stream was incriminated. DeVries used lysolecithin from human serum to produce hemolytic anemia with microspherocytosis in animals (51). The development of the anemia could be inhibited and the anemia neutralized by producing hypercholesterolemia in the animal or by splenectomy. Spleens from patients with hemolytic anemia contain more proteases than normal [Fieschi (52)] but serum showed no significant changes. Nelson *et al.* injected hemolyzed blood and produced in dogs a hemorrhagic syndrome consisting of prolongation of blood coagulation time, gastrointestinal hemorrhages, and death (53).

Hemolysins and hemolytic anemia.—Castle and associates have thrown light on a phenomenon which has been puzzling many investigators (54) It is well-known that hemolysins are difficult to demonstrate in hemolytic anemia. Even the newest methods, which permit the detection of agglutinating antibodies, have added little to the ease of demonstrating hemolysins, the activity of which has to be suspected in view of the clinical and laboratory manifestations of blood destruction. The authors studied the secondary effects of red cell agglutination. From convincingly presented evidence they conclude that red cell agglutination is the fundamental phenomenon and that the course of events is as follows: erythro-agglutination, erythrostasis with local extrusion of serum, tissue ischemia, and release of injurious substances from autolyzing tissues adjacent to stagnating red cells. These observations, though applying directly to hemolytic transfusion reactions, may be responsible also for hemolytic phenomena in other forms of anemia.

Paroxysmal cold hemoglobinuria—Human or guinea pig complement is needed in the cold and warm phases of the Donath-Landsteiner test There is a reciprocal relation between the amounts of complement and antibody needed in the two phases, and also between the amount of complement present and fixation of antibody, as indicated by the titers of the antiglobulin and hemolysin tests (55). The antibody active in the disease is a water-soluble (pseudoglobulin) γ-globulin. The direct Coombs test was positive after attacks induced by chilling, became negative 6 hr after the attack, and re-

turned to positivity a variable number of days later. The titer of the direct Coombs test varied when checked over a period of several months, decreasing with warm weather (56). A false positive Donath-Lansteiner test could be produced by applying cold locally and producing stasis in extremities of healthy people. Intravascular hemolysis was observed [Stich & Korinth (57)]

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of antibodies in excessive amount. Hence, all antiglobulin serums must be carefully checked for prozone reactions before putting them into use (66). Freund's adjuvants have been applied by Emerson and co-workers to the preparation of potent antiglobulin testing serum (67) Heat-killed microbacterium butyricum suspended in sterile mineral oil was one of the recommended adjuvants.

Enzyme-treated red cells.—The sensitivity of the antiglobulin test is equalled and, according to some, even surpassed by the use of enzyme-treated red blood cells Various enzymes, such as trypsin, papain, and ficin are capable of effecting the same results (68). Methods have been suggested to eliminate the occasional false results (69). Strict adherence to time limits of exposure of red cells to enzymes, the use of controls such as enzyme-treated O Rh-negative cells, and normal serums without antibodies (70) make the tests more reliable, more distinct, and the reactions more rapid (71). Enzyme treatment is not suitable for tests for M and N and Duffy factors Some of the other known blood factors are variously affected. Cold agglutinins give higher titers with enzyme-treated cells Wheeler *et al.* have standardized the procedure and established the optimum conditions of testing (72). Wiener & Katz find that on the average titers with enzyme-treated cells are from four to five times as high as those obtained with the serum albumin technique They found no case in which enzyme-treated cells failed to react in the presence of Rh antibodies, but saw cases in which this technique was positive and the other techniques negative (73).

The different enzymes have their advocates. Papain is claimed to be the most satisfactory with regard to sensitivity, specificity, and freedom of prozone reactions (74). Transient but true agglutination of trypsinated cells may be the source of false negative readings, making it necessary to read results within the recommended time limits Enzyme-treated cells absorb more of the antibody than fresh cells, and the absorption increases with the amount of enzyme used (75).

What happens to enzyme-treated red cells that makes them more susceptible to the agglutinin? Ponder found that their volume was slightly increased, up to a maximum of 10 per cent, beyond which longer trypsinization did not further increase the volume With the increase of volume went a decrease in density The electrophoretic mobility of trypsin-treated red cells was reduced (76). A combination of the antiglobulin test with enzyme-treated red cells is claimed as the most sensitive method of detecting Rh antibodies (77).

Placental permeability.—The important question of placental permeability as a factor in the pathogenesis of fetal erythroblastosis continues to attract attention. It seems that placental permeability is only one factor, and the type of antibody is another at least as important The so-called serum albumin agglutinins, the antibody reacting in the presence of high protein concentration but not reacting in a saline medium, have a greater ability to pass through the placenta than so-called saline agglutinins. It is possible

that the antibodies involved in the antiglobulin test pass through the placenta even more readily than serum albumin agglutinins [De Kromme *et al* (78)]. This suggestion was offered to explain the discrepancy between the low antibody titer during pregnancy and the severity of the disease in the newborn in some instances. A high titer of the antiglobulin test and a low titer of serum albumin agglutinins (conglutinins), the so-called high Coombs conglutinin index, is supposed to give a bad prognosis, and vice versa. Also, a high titer of the serum albumin agglutinins by themselves gives a bad prognosis The index may be of value if the serum albumin agglutinins are low. There are, no doubt, variations in the permeability of the placenta itself. Hence, a low titer of antibodies will be much more dangerous to the fetus if the placenta has a high degree of permeability. Both factors play a part. permeability of the placenta and type of antibody.

Rh antiserums.—Electrophoretic studies of so-called Rh blocking antibodies showed that they are associated with a γ-globulin fraction of low mobility. Some of the other forms of Rh antibodies (for example, so-called cryptagglutinoids) were distributed throughout the γ-globulin, and 25 per cent of them were also associated with α- or β-globulin or both [Cann *et al.* (79)] Batson *et al.* offer sodium azide as a good preservative for Rh antiserums. It has no undesirable effect on the agglutinating activity of stored Rh antiserums in concentrations ranging from 0 05 to 0 1 per cent

The increased use of Rh tests brought with it the problem of securing enough testing serum, and hence arose the importance of finding better methods for the production of such antibodies Human volunteers are becoming increasingly important as a source of Rh antiserums There is no satisfactory explanation for the striking variations in the response of different persons to the injections of Rh antigens. It has been claimed that persons with hemolytic anemia have a particular proneness to the development of antibodies of all kinds [Wiener (13)] In accord with this hypothesis are observations like the following A patient with hemolytic anemia received in the course of a month blood from 24 different donors She developed a variety of Rh and other blood group antibodies, such as anti-E, anti-C, anti-M (active at 37°C.), and a cold antibody (81) Another patient, who received 20 transfusions in 12 years, and had a splenectomy, developed nine blood group antibodies Some of them, such as anti-S, anti-E, anti-C^w, anti-K and anti-Le^a, were probably immune antibodies (82) Such examples support the hypothesis of constitutional readiness to produce antibodies On the other hand, the suppression of Rh antibodies continues to attract attention in view of its possible importance for the treatment and prevention of hemolytic disease Sodium salicylate was thought to suppress antibody production, but experiments in man (83) and in guinea pigs (84) showed no such effect. Whenever suppression was noted, it was easily explained by the toxicity of the drug.

Interpretation of Rh antibodies during pregnancy—Interpretation of Rh antibodies during pregnancy is made difficult by the occasional observations

of an increase in the titer during a pregnancy with an Rh-negative fetus. This so-called anamnestic reaction has attracted considerable attention. Schneider and co-workers calculated that it occurs approximately in one out of six of all pregnancies of Rh-negative women (85). These authors claim that it is not possible to distinguish by means of antibody behavior alone between an anamnestic reaction and one indicative of new sensitization

Lucia & Hunt studied 30 cases of normal Rh-negative infants born to previously sensitized Rh-negative mothers. In 17 of the mothers appreciable amounts of Rh antibodies were consistently present; in seven the titer increased in intensity and in 10 remained constant. The basis for the prediction of an Rh-negative infant to be born to a sensitized Rh-negative woman is, first, the determination of the Rh status of the husband (if he is homo- or heterozygous), and second, the trend of the antepartum Rh antibody titer. If the husband is heterozygous and the titer remains constant, it is probable that the baby will be Rh-negative (86). Wiener denies that there is such a thing as an anamnestic reaction and attributes rises observed during pregnancy with Rh-negative babies to faulty technique or to over literal interpretation of results of antibody titrations (87). He maintains that antibodies do not rise when the fetus is homospecific. The argument that there are no reports of nonspecific elevation of Rh antibodies following transfusion of Rh-negative blood cannot be dismissed easily.

Prognosis.—According to Page *et al*, the most important factor determining the prognosis is a history of a transfusion with Rh-positive blood, or of a child previously born with fetal erythroblastosis. In the absence of such information, routine testing for Rh antibodies throughout every Rh incompatible pregnancy is of definite value (88). Five factors should be taken into consideration: (*a*) presence of "blocking" antibodies; (*b*) a significant quantity of antibodies; (*c*) their presence for more than three weeks prior to delivery; (*d*) their presence on every successive test; and (*e*) the presence of ABO compatibility between mother and baby. All these factors aggravate the prognosis When all five were positive, only 2 out of 28 Rh-positive babies escaped fetal erythroblastosis. When one factor was negative, 28 of 30 babies escaped the disease When two factors were negative, all babies were healthy.

According to Mollison & Cutbush, the hemoglobin at birth is prognostically the most important finding. Prematurity was of somewhat secondary importance. Next to anemia was the level of bilirubin. Both determinations should be done on cord blood. A close relationship was found between the bilirubin concentration and the liability to develop kernicterus Of 30 infants with peak bilirubin concentrations not exceeding 18 mg per 100 ml., none developed kernicterus, whereas of 11 infants with peak bilirubin concentrations exceeding 18 mg, five died of kernicterus and two others survived with signs of motor damage (89).

ABO and Rh—The presence or absence of ABO compatibility between mother and infant seems of importance for the probability of the disease. It has been reported by various authors that in the presence of hemolytic

disease of the newborn. ABO compatibility between mother and infant was more frequent (95 per cent) than in an unselected sample of the population (80 per cent) [Lucia & Hunt (90)]. It is possible that ABO compatibility between Rh-negative mother and Rh-positive child may favor development of Rh sensitization in the mother and, later, hemolytic disease in the child. It has been suggested that in the presence of ABO incompatibility between mother and child, Rh-positive blood cells of the fetus entering the circulation of the mother would be much more readily eliminated than if they were compatible with regard to the ABO groups. In this way the opportunity for sensitization would be less readily available. Otherwise there is no relationship between Rh and ABO factors, as is shown again in a sampling of 5,175 women (91). The presence of antepartum sensitization was the most important factor influencing the prognosis. The importance of the five previously mentioned factors with regard to the prognosis of fetal erythroblastosis was tested on 198 instances of sensitized Rh-negative women. There were instances of normal Rh-positive infants born to mothers who showed the presence of all five factors, but there was no instance of an afflicted child born to a mother who lacked two or more of these factors (92). The probability of having a baby with erythroblastosis is greater for a sensitzed Rh-positive mother than for a sensitized Rh-negative woman (93). Two queries in the *Journal of the American Medical Association* present succintly Rh incompatibility problems confronting the practicing physician (94). The whole subject, with special emphasis on its danger and medical, moral, and legal implications, is well presented in a recent monograph [McCurdy (95)]. The present-day knowledge of pathologic changes in hemolytic disease of the newborn has been brought up to date by Lindsay (96). The smaller number of Rh-negative persons among Negroes reduces the incidence of hemolytic disease, but Rh factor incompatibility and its consequences are seen in Negroes with the same results as in white persons [Marsters (97)]

Blood in erythroblastosis.—Erythrophagocytosis was reported in many isolated instances, but Cooper found it in 25 of 27 cases, employing a careful and painstaking method of study (98).

Differential diagnosis—Inclusion body disease may present great differential diagnostic difficulties in fetal erythroblastosis (99). This disease, when occurring in stillborn infants and in infants dying soon after birth, presents clinical manifestations similar to those seen in fetal erythroblastosis, including jaundice, purpura, and erythroblastemia It is caused by a virus similar to the one known as the salivary gland virus of rodents Characteristic pathologic lesions have been observed, but it is obvious that the differential diagnosis may not be easy, and it is in such cases that the study of blood group factors may be important [Wyatt *et al.* (100)].

Fetal erythroblastosis in animals—This disease was observed and produced in dogs, donkeys, and various other animals At least six different blood groups have been found in dogs: A, B, C, D, E, and F [Young *et al* (101)]. Most of these have been produced by prolonged immunization. In A-negative

of an increase in the titer during a pregnancy with an Rh-negative fetus This so-called anamnestic reaction has attracted considerable attention Schneider and co-workers calculated that it occurs approximately in one out of six of all pregnancies of Rh-negative women (85). These authors claim that it is not possible to distinguish by means of antibody behavior alone between an anamnestic reaction and one indicative of new sensitization.

Lucia & Hunt studied 30 cases of normal Rh-negative infants born to previously sensitized Rh-negative mothers. In 17 of the mothers appreciable amounts of Rh antibodies were consistently present; in seven the titer increased in intensity and in 10 remained constant The basis for the prediction of an Rh-negative infant to be born to a sensitized Rh-negative woman is, *first, the determination of the Rh status of the husband (if he is homo- or* heterozygous), and second, the trend of the antepartum Rh antibody titer. If the husband is heterozygous and the titer remains constant, it is probable that the baby will be Rh-negative (86). Wiener denies that there is such a thing as an anamnestic reaction and attributes rises observed during pregnancy with Rh-negative babies to faulty technique or to over literal interpretation of results of antibody titrations (87). He maintains that antibodies do not rise when the fetus is homospecific. The argument that there are no reports of nonspecific elevation of Rh antibodies following transfusion of Rh-negative blood cannot be dismissed easily

Prognosis.—According to Page *et al*, the most important factor determining the prognosis is a history of a transfusion with Rh-positive blood, or of a child previously born with fetal erythroblastosis. In the absence of such information, routine testing for Rh antibodies throughout every Rh incompatible pregnancy is of definite value (88). Five factors should be taken into consideration: (*a*) presence of "blocking" antibodies; (*b*) a significant quantity of antibodies, (*c*) their presence for more than three weeks prior to delivery, (*d*) their presence on every successive test; and (*e*) the presence of ABO compatibility between mother and baby. All these factors aggravate the prognosis. When all five were positive, only 2 out of 28 Rh-positive babies escaped fetal erythroblastosis. When one factor was negative, 28 of 30 babies escaped the disease. When two factors were negative, all babies were healthy.

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Treatment of Fetal Erythroblastosis

Exchange transfusion.—This form of therapy occupies the center of attention. Especially encouraging are reports like that of Wiener, who saw no instance of kernicterus in 30 cases treated with exchange transfusions, as compared with 16 per cent, or four cases in a series of 25 treated with simple transfusions (105). The importance of the titer of Rh antibodies in the mother during pregnancy is pointed out by the finding that with a titer up to four the percentage of stillbirths in Rh-positive babies was 16 7, with a titer of 1·64 the percentage was 30 6, and when the titer was higher than 64, the incidence was 54 5 per cent. With exchange transfusion, the mortality was 15.4 per cent in 78 cases, as compared with 70 8 per cent in 24 siblings born in the same family, and with 31.6 per cent in 19 treated with simple transfusions.

The outlook for babies delivered by Cesarean section is not good. The mortality was 50 per cent, as compared with 7.6 per cent in 66 cases delivered spontaneously or with medical induction Medical induction in Wiener's experience did not tend to give bad results.

An even larger series of 368, live-born, Rh-positive infants of sensitized Rh-negative mothers, showed no kernicterus when treated with exchange transfusions [Allen *et al* (106)]. The factors determining the presence of kernicterus were jaundice, immaturity, high maternal antibody titer, male sex, and family history of previous occurrence of kernicterus in a child Jaundice was the common denominator of all of the previously mentioned factors Exchange transfusions prevented kernicterus by lessening the jaundice The authors repeat the claim of favorable results obtained with female Rh-negative blood in exchange transfusions They recommend a second exchange transfusion if jaundice increases following the first, early administration of the blood, and avoidance of early induction of labor The last recommendation is in contrast to the previously reported experience of Wiener After this program of treatment was instituted, they had only one case of kernicterus in a group of 109 babies with erythroblastosis in an infant who did not receive a second exchange transfusion This result is impressive in view of the opinion of authorities that kernicterus may be expected to occur in approximately 35 per cent of markedly jaundiced, erythroblastotic babies if not treated with exchange transfusion Indications for exchange transfusion are (*a*) if there is a clear-cut diagnosis of fetal erythroblastosis (Rh-postive baby of a sensitized Rh-negative mother showing jaundice, hepatosplenomegaly, edema, or a red count of less than 4½ million red blood corpuscles); (*b*) if there are no clinical signs, but the maternal Rh antibody titer is high (in their laboratory 1:16 or higher), (*c*) if the baby is premature, especially less than 38 weeks gestation, because this type of baby is more inclined to develop jaundice, or (*d*) if there is a history of fatal or serious erythroblastosis in a previous infant All other things being equal, they are a little more radical in the case of a male infant. Diamond and associates (107) summarized their experience in the use of exchange transfusion

bitches immunized by intravenous injections of A-positive blood and mated with A-positive sires, there was a drop of anti-A during pregnancy and a marked increase of anti-A in colostrum, more than in maternal serum A-positive pups showed hemolytic disease provided they suckled the immunized bitch during the first day of life. Anemia and increased osmotic fragility of red cells of A-positive pups became apparent within 16 hr. after birth, but if pups were fed cow's milk during the first 16 to 24 hr. of life before suckling an immunized bitch, they did not show anemia Pups born to non-immunized bitches developed the disease when allowed to suckle an immunized bitch during the first few hours of life. The same procedure with factors C or E did not produce hemolytic disease, although the breast milk contained anti-C or anti-E soon after birth. Etcheverry observed hemolytic disease in the offspring of five mares which had potent agglutinins reacting specifically with the red cells of the sick animals (102). He also observed regularly specific blood groups in horses. This report and several previously reported studies of similar findings in various animals round out the isoimmunization hypothesis of the pathogenesis of fetal erythroblastosis.

Fetal erythroblastosis caused by ABO blood factors—There has been considerable controversy regarding the existence of such an entity. The main difficulty arises from the fact that anti-A and anti-B isoagglutinins are present naturally and are difficult to differentiate from those resulting from isoimmunization. Witebsky (205) showed recently that the naturally occurring isoagglutinins can be distinguished from those resulting from immunization by using human serum as diluent. In the presence of immune antibodies, the titer in a test employing the human serum as diluent is higher than with saline. The reason for the relative infrequency of erythroblastosis caused by factors A and B is probably, at least in part, the fact that blood group factors A and B do not produce incomplete antibodies as readily as does the Rh factor Only incomplete antibodies are passing through the placenta quantitatively. In cases where the infant is Rh-negative, the titer of incomplete antibodies in the maternal and cord serum were found to be identical [van Loghem *et al* (103)] When the infant was Rh-positive, the titer was lower or the incomplete antibodies could not be detected in the umbilical

nins by other tissues than blood cells is probably another factor explaining the relative rarity of this form of the disease It has been noted that in cases of fetal erythroblastosis caused by AB blood factors, the antiglobulin test was, as a rule, negative or feeble This may result, at least partly, from the fact that the antibody attaches itself more readily to tissues, including the placenta, liver, and spleen, which contain large amounts of the corresponding antigen. Spherocytosis and increased hypertonic fragility were found in cases of erythroblastosis arising from AB incompatibility [Robinson *et al.* (104)].

hematocrit to 50 per cent [Veall & Mollison (114)]. These authors recommend concentrated red cell suspension instead of whole blood. They arrived at their conclusion using red cells labelled with P^{32}. A similar technique was used by Wasserman and associates (115). They developed formulas for replacement transfusions in adults, which can no doubt be used with similar effectiveness in infants.

An interesting statistical study of 74 cases treated with exchange transfusion showed that the mortality was considerably higher (21.9 per cent) in a group in which the diagnosis of the disease was made or suspected antepartum, whereas it was only 4.3 per cent in cases diagnosed after birth, in other words, in cases which would have to be considered as neglected [Wiener & Wexler (116)]. The explanation is offered that in the first group the diagnosis was made with the help of the history, namely, the presence of previous stillbirths and fetal erythroblastosis, indicating that the handicap of such a background can be overcome only with difficulty by therapeutic measures.

Early termination of pregnancy.—There seems to be little doubt according to the reports presented that Cesarean section aggravates the outlook in fetal erythroblastosis. However, there are differences of opinion regarding the advisability of other forms of medical termination of pregnancy. As already mentioned, Diamond and his group are against such termination, while Wiener is for it. Schneider and associates (85b) came out against early termination of pregnancy, medical as well as surgical. According to Dahr (117), interruption of pregnancy should be permitted only in a woman who already has given birth to at least one dead infant, with a rapidly increasing titer up to the end of the fourth month of pregnancy, and who during the first two months of pregnancy had no Rh antibodies in her blood. If absence of blocking antibodies has not been demonstrated during the interval between the two pregnancies, or during the first two months of the new pregnancy, interruption of pregnancy should not be considered because such Rh antibodies may be simply a carry-over from a previous pregnancy. According to Dahr (117), sterilization of a woman may be permissible from a social point of view, provided that there have been several stillbirths and that the birth of a healthy child can no longer be expected But even in such cases, although sterilization could be legally permissible, medically it is not justifiable because it is possible for such a woman to give birth to a healthy child conceived from a heterozygous, Rh-positive man or an Rh-negative man. This statement brings up the question of artificial insemination, which is discussed by McCurdy (95) In this monograph, the medical, moral, and legal implications of sterilization, therapeutic abortion, and adoption are treated exhaustively. It seems that at least one court has found Rh sensitization grounds for divorce, maintaining that husband and wife are not sterile and could have children with other spouses of compatible Rh type (94a).

Prevention of erythroblastosis—A recent attempt to try ethylene disulfonate was not successful (118) The substance exerted no influence on antibody production and had no apparent effect on the disease of the newborn.

in more than 350 erythroblastotic infants. They use the umbilical vein, blood of group O, female donors. They add soluble AB substances to the blood if the infant is of a different group than O. If the mother is Rh-negative, they use Rh-negative donor blood; if the mother is Rh-positive, they use blood not agglutinated by her serum. Brancato's mortality in a series of 24 cases treated with exchange transfusion was 16 7 per cent. The outcome differed depending on several factors. All babies without abnormal past obstetrical history or a history of blood transfusion in the mother recovered; mortality was 33.2 per cent in cases with an abnormal history or history of blood transfusion (108).

Female blood transfusions.—The beneficial effect of female blood claimed by Diamond has not been confirmed by Sacks *et al.* (109). A pair of identical male twins with erythroblastosis offered a unique opportunity to study comparative effectiveness of exchange transfusion and multiple small transfusions (110) Twin A was more icteric, had a splenomegaly and hepatomegaly, and appeared to offer a poorer prognosis It was given an exchange transfusion, followed by two small transfusions Twin B, also severely jaundiced but less anemic and without clinical enlargement of liver and spleen, received three small transfusions. Twin A recovered more rapidly than B, whose weight increased more slowly and whose jaundice persisted for four weeks However, at nine months, twin B was more advanced in motor development, whereas twin A showed slight weakness of extremities Exchange transfusion is widely used throughout the world, judging by reports All of them emphasize the importance of early treatment [Mellone (111)]. Again and again one reads reports showing undesirability of terminating pregnancy by Cesarean section in cases of fetal erythroblastosis [Bromchil & Leon (112)]. Van Loghem (64) states that exchange transfusion is more likely to be useful when the antibodies of the mother have combined mainly with the red cells of the infant, than if they attach themselves to the tissues. In the latter case, the Coombs test will be weaker, while in the former it will be stronger. He compares the incomplete antibodies in the umbilical cord with those in the maternal blood. A marked difference between the two is indicative of the amount of antibodies attached to the tissues of the infant

Occasionally one sees what appears to be an ill effect of adult blood used for replacement transfusion It has been suggested that this apparent effect may be produced by the presence of a substance in the adult plasma which favors agglutination and which is absent in the blood of the newborn Both high protein content and so-called "conglutinating" activity of adult blood are unphysiologic for the newborn infant It has been recommended that erythrocytes suspended in plasma, diluted with sodium chloride solution to the average physiologic protein level of newborn infants, be used for exchange transfusion [Seelich *et al.* (113)] A nomogram was constructed from which one can compute how much blood is to be used for the exchange transfusion in order to reduce the hematocrit of Rh-positive cells in the infant to 5 per cent and to add sufficient Rh-negative cells to bring the total venous

in circulating antibodies, although subsequent injection of Rh-positive cells was followed by a distinct rise in titer. Injection of as much as 1½ gm of elinin intramuscularly failed to reduce circulating Rh antibodies.

ACTH.—In view of the successful application of ACTH in treatment of hemolytic anemia, the report of two cases of erythroblastosis in which ACTH was tried is interesting In the first case, a replacement transfusion was also used in a severely anemic infant with all other manifestations of erythroblastosis. In the other case, ACTH was given by itself, at first 12.5 mg. at 12-hr. intervals for three days, then 8 5 mg. every 8 hr. for two days, and finally 6 25 mg every 8 hr for 48 hr. The icterus disappeared, the erythrocyte count went up, and the baby recovered without transfusion (126).

Physiologic jaundice—According to Wexler & Wiener, physiologic jaundice is not caused by blood incompatibility but by cold agglutinins and is facilitated by exposure of the child to chilling (127). The hypothesis is supported by the regular presence of cold agglutinins during pregnancy and by the fact that these cold agglutinins are claimed to give better reactions in protein-rich mediums They are monovalent in Wiener's terminology. Such antibodies are known to be particularly prone to pass through the placenta. It is possible that the action of the cold agglutinins is enhanced by the poor temperature control in newborn infants, especially in the premature. It should not be too difficult to check the validity of this hypothesis.

BLOOD AND PLASMA TRANSFUSIONS

The convincing demonstration by Castle *et al.* that hemolysins play a relatively minor role in hemolytic transfusion reactions and that the major part is played by agglutinins was discussed previously (54). This explanation clarifies the puzzling observations that hemolysins could so rarely be detected during and after transfusion reactions

Transfusion reactions—One cannot help wondering sometimes how we got along in the pre-Rh days, when we must have frequently given Rh-positive blood to Rh-negative recipients The number of reactions observed at that time was certainly much smaller than the number of such transfusions This question seems to be explained by a report of 15,819 transfusions, among which 23 recipients were falsely diagnosed as Rh-positive and given from 1 to 29 pints of incompatible Rh-positive blood [Klein *et al.* (128)] No hemolytic transfusion reactions were observed, although 70 per cent of the patients showed sensitization in the form of Rh antibodies. The authors concluded that there must be some protective mechanism against reactions in Rh sensitized patients Large quantities of blood group specific substances A and B were not responsible for untoward reactions in recipients of blood transfusions, and repeated injections did not produce clinical sensitivity [McNeil *et al.* (129)] These substances are used to neutralize anti-A and anti-B agglutinins in the blood of so-called universal donors (of group O). On the other hand, severe hemolytic transfusion reactions have been

On the other hand, ascorbic acid was found to be capable of inhibiting Rh agglutination [Traina (119)]. Traina assumed that ascorbic acid acts on the red blood cells, neutralizing the Rh agglutinogen. It remains, at least for the time being, that the only promising way of preventing erythroblastosis in the primipara is to use homologous Rh blood for transfusions Experience here and abroad confirms that a large number of cases of erythroblastosis *in first born babies is the result of incompatible Rh transfusions* given to mothers (111).

Hapten.—Prevention of erythroblastosis could be accomplished in one of several ways: (*a*) blocking the passage of antigenic substances from the fetus through the placenta to the mother; (*b*) prevention of antibody development in the mother in response to the antigen of the fetus; (*c*) blocking the passage of antibodies from the mother through the placenta to the fetus; (*d*) neutralization of the antibodies produced in the mother by injection of a substance capable of producing that result. Carter attempted to accomplish the last objective with the help of a preparation known as hapten, which is supposed to have the ability to combine with and neutralize the antibodies without stimulating production of more antibodies (120). Goldsmith treated 26 women throughout pregnancy; 16 gave birth to normal, healthy Rh-positive infants. He emphasizes the necessity of starting the treatment early during the first trimester, or preferably before the conception (121). Most of the other writers failed to find anything to recommend its use. Attempts to produce the hapten according to Carter's instructions failed, apparently because the Rh antigen was destroyed during the first extraction with 95 per cent alcohol Howe and associates (122) found "absence of any demonstrable *in vitro* Rh specificity in lipid extracts prepared by Carter's method" and concluded that "administration to Rh sensitized pregnant women has no clear therapeutic rationale." Clinical evaluation of the hapten was equally discouraging It had no influence on the lowering of the titer of the antibodies during pregnancy, even when the fetus turned out to be Rh-negative and, therefore, the rise of the antibodies was not the result of stimulation by a specific antigen. It failed to reduce antibodies in women not pregnant at the time of treatment [Hamilton & Brockland (123)] There was no evidence whatsoever of any beneficial effect, on the clinical course of the disease in the newborn, of the administration of hapten to mothers. Similar results were reported by others. Wolf and associates (124) claim that the substance as prepared according to Carter is a hapten, although of "exceedingly low potency."

Careful chemical study of a fraction called elinin revealed the presence of A, B, and Rh factors (125) Evans and co-workers (125) were unable to reproduce the results of Carter Elinin, a lipoprotein fraction of red cells, has the ability to inhibit Rh_o (D) and rh′ (C) antibodies, only when prepared from Rh-positive cells This activity was destroyed by heating to 56°C. Solutions of elinin with *in vitro* Rh activity failed to produce Rh antibodies in rabbits and guinea pigs. Injection into man failed to stimulate an increase

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of blood donors at the nailbeds. The dye can be detected with ultraviolet light up to about three weeks [Hoyt *et al.* (139)].

Use of blood fractions—It may be advantageous at times not to use whole blood but only red cells or even leukocytes. Use of red cells, packed or washed, is sometimes more economical and frequently better tolerated, especially in hemolytic anemia.

Julliard *et al.* describe also beneficial effects in some cases following the use of concentrated suspensions of leukocytes (140). The technique of preparation of such suspensions is included. The difficulty of raising the white blood cell count by transfusion is well-known, and the reason for it seems to be the tendency of the injected leukocytes to accumulate in the lungs [Weisberger *et al* (141)]. The function of the liver and spleen in the removal of leukocytes is much less pronounced.

Transfusion of blood platelets.—A patient with thrombocytopenia received blood from a patient with polycythemia whose platelet count was about eight times the normal. The transfused platelets survived and fulfilled their normal, physiologic function for from five to six days [Hirsch *et al.* (142)].

Advantages of intra-arterial transfusions have been pointed out, especially in shock in which rapid return to normal blood pressure and early re-establishment of renal function are especially desirable (143, 144). Hemolytic transfusion reactions have been treated successfully by exchange transfusions [Wiener & Katz (145)].

Blood transfusion as a method of study—This procedure has become increasingly important, especially in the study of hemolytic anemia. It helps to determine whether the abnormality is in the red cells or in the plasma [Hamilton *et al.* (146)]. The original Ashby technique has been modified and improved DeGowin writes about the so-called inagglutinable cell count (147). Stats' new method employs agglutination and subsequent sedimentation of the red blood cells, and instead of counting, the process is carried out by addition of an agglutinating serum specifically selected so that it clumps the injected cells or the cells of the host (148).

Transfusion in animals has been used for the detection of new blood factors. The discovery of the Rh factor is an example. Recently six blood groups in dogs have been detected in this way [Young *et al.* (101)]. Also, blocking antibodies similar to blocking antibodies seen in man have been produced by transfusions of blood of pigs into other pigs differing in composition of their blood groups [Kuhns (149)]

New Blood Groups

The Rh factor initiated a period of progress in the detection of blood group specific antibodies. These advances, as well as the continued increase in the use of blood transfusions, have led to the discovery of new blood factors. The circumstances of these discoveries are frequently quite similar. Usually, the patient has received many blood transfusions and manifests a new type of antibody in the serum With the help of these antibodies, new

observed following transfusions of group O blood or plasma and have been attributed to the presence of immune isoagglutinins [Ervin *et al.* (130)]. The anti-A isoagglutinins in the blood responsible for such a transfusion were shown to fix complement to act as hemolysins, and were difficult to neutralize with soluble A group specific substance. This behavior of isoagglutinins is considered characteristic of immune antibodies. Approximately from 10 to 20 per cent of so-called universal donors contained immune antibodies. Reactions caused by blood of dangerous universal donors are not so readily recognized as those which arise from the injection of incompatible red cells because they are somewhat slower in developing and sometimes may occur without some of the usual manifestations such as chills, fever, circulatory collapse, back pain, oliguria, hemoglobinuria, or jaundice.

Homologous serum jaundice.—The danger of homologous serum jaundice seems to have been reduced but not eliminated by ultraviolet radiation of plasma [Blecher (131)]. It may be that irradiation is an unnecessary procedure if the observation by Allen and associates is confirmed (132). They found that keeping the plasma at room temperatures destroys the virus. In their experience at the University of Chicago, of 212 patients who received only plasma, none developed hepatitis, whereas of 652 who received only blood, or blood as well as plasma, 17 developed hepatitis. Danger to medical workers from contact with infected plasma is emphasized by a recent report in which the disease was contracted during embalming of the body of a patient who had died of hepatitis (133).

Plasma transfusion reactions.—It is possible that the transfusion reactions which are seen in patients given plasma transfusions may be the result of a factor involved in the process of coagulation [Crosby & Stefanini (134)]. Sometimes patients not tolerating whole blood may react better when given only washed red cells [Dameshek & Neber (135)]. A heat labile plasma fraction is postulated as a cause of this reaction. A technique was described (provocative plasma test) which helps to detect the susceptible individuals. To the list of diseases transmissible by transfusion, disseminated inclusion disease has been added as a new distinct possibility [Wyatt *et al.* (100)]. Leukopenia was seen immediately following blood transfusions with drops to as low as 1,500 white cells from the original of 7,200 [Bucher (136)]. The reaction is thought to be caused by particles of fibrin.

Donors.—The effect of withdrawal of 500 ml. of blood was not noticeable in hematologic or chemical changes in the peripheral blood [Litwins *et al.* (137)]. Pulitano & Gaetano report a long range study of 91 professional donors, of whom some had been giving blood for several years with the number of donations ranging from 10 to 207 (138). There were no noticeable, unfavorable effects in body weight, general health, arterial blood pressure, or morphology of the blood. It is recommended that donors be given a diet rich in proteins and iron. It is sometimes difficult to protect a donor against his desire, whatever its motivations, to give blood too frequently. Therefore, it has been recommended that a fluorescent dye be used to mark the fingers

of blood groups in animals. Six blood groups have been found in dogs immunized with repeated transfusions (Young *et al.* (101)].

INFECTIOUS MONONUCLEOSIS

Two developments stand out in the modern conception of infectious mononucleosis as it emerged from studies of the last few years: (*a*) it is a systemic disease involving practically all tissues of the body to a varying extent; (*b*) it is by no means the harmless disease it was thought to be.

Changes in the liver.—The organ especially severely involved is the liver. This information was gained from the study of autopsies on some of the patients who died of what was thought until recently to be a perfectly benign and insignificant malady. Biopsy studies have further added to the information. Kass & Robbins (156) reported a case which is a good illustration of the points mentioned in the introductory sentences. A young girl died suddenly, after a relatively brief illness during which she worked all the time, and only 2 hr. after she was seen by her physician, who thought that there was nothing serious the matter with her. The autopsy showed rupture of the spleen with a massive abdominal hemorrhage as the cause of death. Microscopically, typical changes were found in the liver, spleen, lymph nodes, and heart. The authors discuss the discrepancy between the extensive changes in the liver and the fact that according to them no cases of infectious mononucleosis have been reported showing cirrhosis following the disease This finding they explain as a result of the fact that the tissue changes in the liver in infectious mononucleosis do not tend to necrosis Interestingly, another case was reported in a 24-year-old male who developed cirrhosis of the liver during a three-year observation period following infectious mononucleosis [Leibowitz & Brady (157)] It may well be that in this case the cirrhosis is not necessarily the result of infectious mononucleosis because there was a complicating nutritional and alcoholic history On the other hand, the accelerating and contributory role of infectious mononucleosis cannot be excluded.

A possible relationship between virus hepatitis and infectious mononucleosis has been suggested by the presence of similar abnormal lymphocytes in both diseases, by the multiplicity of abnormal liver function tests in infectious mononucleosis, and finally, by tissue changes revealed in biopsy specimens and autopsy material. Jordan & Albright studied 24 consecutive cases of infectious mononucleosis and employed many liver function tests (158). The results were positive in 83 per cent of cases with the thymol turbidity test, in 79 per cent with the cephalin flocculation test, and with decreasing frequency in the bromsulfalein, urine urobilinogen, alkaline phosphatase, and serum bilirubin tests There was no relation between the abnormal liver function tests, signs and symptoms of hepatic involvement, and height of the antibody titer. The authors concluded that from two-thirds to three-fourths of patients with infectious mononucleosis have hepatitis. The experience of others gives even higher figures. Ninety per cent of 90 patients showed abnormal hepatic function [Bennett *et al.* (159)]. The hepatic

factors are being recognized. A rather characteristic example is the report of a patient who received 20 transfusions and who was found to have seven so-called irregular blood group antibodies in her serum, namely, anti-N, anti-S, anti-E, anti-C^w, anti-K, anti-Le^a, anti-Le^b, in addition to her regular isoagglutinins anti-A and anti-B [Collins *et al.* (82)]. In other instances, one or more pregnancies are responsible Here belongs the case of a woman who developed, after several pregnancies, an antibody against the newly discovered factor known as Kell. She also had several blood transfusions following a postpartum hemorrhage in her first pregnancy [Cochrane *et al.* (150)] The Kell factor has been found responsible for at least 17 cases of fetal erythroblastosis. A recent report shows the danger of using the husband's blood for transfusion. In this case, the woman was given several small injections of the husband's blood, 20 ml each, as a therapeutic measure. Eventually she developed a rather strong anti-Kell agglutinin and had several miscarriages [Prokop *et al.* (151)].

A new blood factor was discovered by Levine and associates. It was responsible for fetal erythroblastosis of the newborn and was labelled Ml, using the name of the donor of the antibodies that led to the discovery of the new factor This antigen is apparently rare It was present in four members of three generations of the same family, but was not found in 425 random specimens (152). Another most unusual new blood factor, labelled Tj^a, was detected with the help of an antibody found in the blood serum of 64-year-old type O, Rh-positive woman with a gastric carcinoma Her serum was found incompatible with 3,000 random, group O individuals The factor could be demonstrated in the blood of the patient's husband and their four children, and in the blood of four children of her sister The same blood factor was also found in the patient's gastric tumor [Levine *et al.* (153)] Levine speculates that this factor, which was present in the patient's tumor but absent in her red cells, may have arisen in the tumor by means of a mutation Recently, antibodies of the same variety were found in a woman living in South Africa (153)

Blood group O, which was originally thought to be merely characterized by the absence of factors A and B, is known to have a specific group factor. Immune serums can be produced which specifically react with this factor. Formaggio studied the maturation of this factor in the human infant and found its behavior similar to that of the other factors It is gaining in strength from birth until it reaches almost adult potency at the age of five (154) The ability to taste phenylthiocarbamid, an extremely bitter substance, is absent in about 30 per cent of all individuals and present in the others The ability to taste this substance is determined by a dominant mendelian characteristic (P) and nontasting is a recessive (p). It has been applied to exclusion of paternity on the basis that if the offspring is a taster, at least one parent must be a taster. This property is present in the newborn infant in the same distribution as in the adult [Cardullo & Holt (155)]

Blood groups in animals.—Transfusions have been used for the detection

recently. Hovde & Sundberg (167) found in 9 of 23 cases of infectious mononucleosis, epithelioid cells in marrow smears and foci of granulomatous inflammation in sectioned particles. The lesions resembled those seen in brucellosis, and to a lesser extent, those of sarcoidosis and tuberculosis.

X-ray findings.—Arendt described diagnostic problems which may present themselves during a roentgenologic study of patients with infectious mononucleosis There may be enlarged mediastinal lymph nodes or, occasionally, changes suggestive of congenital heart disease or, finally, pulmonary changes simulating atypical pneumonia (168).

Complications.—In view of this widespread involvement, it is not surprising that an increasing number of complications have been reported. Another case of thrombocytopenic purpura was observed [Angle & Alt (169)] This is the seventh case of the same complication. Two cases of acute hemolytic anemia have been reported recently (20, 170). The last case was in a 17-year-old Negro girl with typical infectious mononucleosis, as well as with anemia and spherocytosis and other manifestations of blood destruction. There was no evidence of sickle-cell anemia The Coombs test, direct as well as indirect, was strongly positive. The patient recovered within a month, but it took several months before the serologic test for infectious mononucleosis and the Coombs test became negative. Hemolytic anemia seems to be a not infrequent complication of infectious mononucleosis. A case of frank hematuria was also reported recently with complete recovery (171) A subacute, granulocytic leukemia followed a case diagnosed as infectious mononucleosis in a man of 20 (172). The transition took place under the eyes of the physician, within a period of about six weeks. It is regrettable that in this and in similar cases the serologically specific differential test was not done. The patient died of leukemia about 3½ months from the onset of infectious mononucleosis

A fatal case of infectious mononucleosis resulting from a rupture of emphysematous bullae and a sudden pneumothorax on the thirty-eighth day of illness in a man of 22 was reported by Sharp (173) A positive presumptive test was present during life Another complication in a severe anginose type requiring tracheotomy was also reported [Librach (174)] Muller, in his exhaustive recent review, emphasizes that there is a tendency to frequent involvement of the pharynx in recent years (175).

The statement seen occasionally in the literature that infectious mononucleosis is rare in the Negro is not borne out by actual experience The previously mentioned case of hemolytic anemia in the Negro girl, and another case reported by Rathmell and associates (176) add to the series of over 70 cases of the disease reported in Negroes.

The differential test—The widespread systemic involvement, with resulting interference with the normal functions of various organs, and the strange serologic behavior of the blood such as occasional false positive tests for syphilis, occasional elevated Weil-Felix agglutination titers, increases in serum staphylococcal antitoxin, and increases in agglutination titers with

manifestations, including jaundice, may be extremely severe [McGreevey (160)] Leibowitz studied 65 patients with virus hepatitis and concluded that virus hepatitis and infectious mononucleosis are different diseases (161). He emphasizes that the differential diagnosis between the two diseases may offer difficulties and, therefore, the differential test for infectious mononucleosis may be of deciding diagnostic importance.

Heart.—Electrocardiographic changes with a pattern seen in acute, benign pericarditis were reported in a 17-year-old youth with infectious mononucleosis with an episode of chest pain [Boehm *et al.* (162)]. A normal tracing was obtained after a serial study showed gradual disappearance of the electrocardiographic abnormalities.

Nervous system.—Involvement of the central and peripheral nervous systems has also come to be recognized as a not too infrequent complication of infectious mononucleosis. Bernstein and associates reviewed the literature and state that nervous system involvement occurs in about 1 per cent of patients with the disease. Serous meningitis, encephalitis, meningeal encephalitis, polyneuritis, and peripheral nerve involvement have been described. The cerebrospinal fluid shows an increase of lymphocytes and of protein The prognosis is good as a rule (163) Infectious mononucleosis should be kept in mind when central nervous system manifestions occur which are otherwise difficult to explain. The serologic test for infectious mononucleosis, and especially the differential test, are of great value in such cases. The authors have modified the technique of the test and found it positive in cerebrospinal fluid in their cases, in some cases even when there was no clinical evidence of nervous system involvement The test showed behavior characteristic for the positive differential test, namely, removal of the antibodies with beef cell antigen, but not with guinea pig kidney antigen. In another case, a young man of 21, there was involvement of the optic nerve with papilledema bilaterally, a serous meningitis, and encephalomyelitis [Piel *et al.* (164)]. This example is another illustration that infectious mononucleosis is not always the benign disease it formerly was considered to be. Convulsions and stupor preceding the general manifestions of the disease, severe myelitis, a relapse with convulsions, and facial diplegia after the second week of illness, have been reported in three patients, all of whom recovered [Silversides & Richardson (165)] Eight fatal cases from neurologic complications have been reported Hubler *et al.* (166) describe bizarre neurologic manifestations including coma, respiratory difficulty, and convulsions in a 17-year-old young man in whom the true diagnosis was made with the help of a blood smear and the serologic test (the presumptive and differential tests were positive) The authors recommend consideration of infectious mononucleosis when the diagnosis of encephalitis of an undeterminate type is being entertained in an adult patient It is obvious that without the blood study, and especially of the serologic test, it would not have been possible to make the correct diagnosis.

Marrow—No characteristic marrow changes have been reported until

Vaughn (185) reported a modification of the technique of Maloney & Malzone, which he recommends as a screening test In 17 cases of infectious mononucleosis, the tests were all positive except one, which gave also a negative presumptive tube test. The test is supposed to save time.

Infectious lymphocytosis.—Infectious lymphocytosis, described originally by Smith in 1941, may have to be differentiated from infectious mononucleosis and occasionally from lymphatic leukemia [Lemon & Kaump (186)] Its course is usually mild and it is recognized often accidentally in the course of a blood examination. The serologic test for infectious mononucleosis is negative, the blood findings are those of a lymphocytosis, with absence of cells characteristic for infectious mononucleosis. An epidemic of infectious lymphocytosis in five children of the same Negro family was described by Moyer & Fisher (187). The white counts ranged up to 79,000. There was no enlargment of lymph nodes or of the spleen. The presumptive test for infectious mononucleosis was as high as 112, a titer which could have required the differential test for infectious mononucleosis In young adults the disease may have to be differentiated from chronic lymphocytic leukemia.

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

Since the discussion of the subject by Finch (188) in the preceding volume of this publication, considerable additional information has accumulated on the so-called LE phenomenon. Barnes *et al* (189) discuss terminology, which has become somewhat confused in spite of the relatively short time since the original discovery One differentiates now the LE-phenomenon, cell, body, rosette, and the substance which is responsible for all these is called the LE factor [Haserick (190)] The LE factor is stable and even has a tendency to increase its potency in plasma or serum, but is destroyed by bacterial invasion, by bacterial contamination, or by heating at 65°C., and is inhibited by *p*-aminobenzoic acid but not by cortisone, testosterone, estradiol, and progesterone. It was demonstrable with the postmortem serum and was not influenced by splenectomy [Berman *et al* (191)] The serologic specificity of the LE phenomenon was demonstrated by immune serums produced in rabbits with γ-globulin from plasma of patients with acute lupus erythematosus. Antiserums produced similarly with normal human serum and with normal human γ-globulin were used as controls The LE phenomenon was not demonstrable with previously positive serum after it was mixed with anti-LE γ-globulin rabbit serum, but the serum remained potent when antinormal human serum or antinormal human globulin rabbit serum was added [Haserick & Lewis (192)] Active neutrophils, bare lymphocytic nuclei, and the LE factor in serum were necessary to produce the LE phenomenon [Moyer & Fisher (193)] Addition of a frozen suspension of lymphocytes containing bare nuclei accelerated the phenomenon and made it appear in 15 min.

According to evidence available, the LE phenomenon is not specific qualitatively for acute disseminated lupus It was not found in rheumatic

Listeria monocytogenes, add up to make infectious mononucleosis a complex disease. In view of that fact, it is fortunate that there is available a highly specific and easily performed serologic test which establishes the diagnosis of the disease in an overwhelming majority of cases. Carpenter and associates (177) found an elevated titer of sheep agglutinins in three instances of monocytic leukemia. In two of them the differential test showed a pattern not characteristic for infectious mononucleosis and helped to establish the correct diagnosis. The characteristic pattern for infectious mononucleosis is the failure of the guinea pig kidney suspension to remove all the antibodies and their removal by the beef cell antigen. Lämmler (178) reported that in none of 34 cases admitted to the hospital had the right diagnosis been made by the physicians sending in the patients. Twenty per cent of the patients admitted as diphtheria turned out to be infectious mononucleosis. In 55 patients with various lymphomas, including 29 cases with Hodgkin's disease, the differential test helped to eliminate what seemed to be false positive tests for infectious mononucleosis in several cases. In a case of what was diagnosed as Guillain-Barré's syndrome complicating infectious mononucleosis, the latter diagnosis was made on the basis of the morphologic blood examination. It would have been much more convincing had the differential test been made [Klovstad (179)]. The paper by Leibowitz (161), previously referred to, brings out the importance of the differential test in the diagnosis of infectious mononucleosis and the separation from viral hepatitis.

It was found recently that human red cells modified by absorption and elution of Newcastle disease virus are agglutinated by serum of patients with infectious mononucleosis to a higher degree than by serum of patients without that disease [Evans (180)]. Elevated titers were also found in serums of 40 cases of viral hepatitis. These findings emphasize further the necessity of using the specific test for infectious mononucleosis, which was found negative in hepatitis.

Eosinophilia.—Kaufman (181) reports that eosinophilia during the acute stage of infectious mononucleosis is not rare. In 41.5 per cent of his own series, there were 4 per cent or more eosinophils and 26.8 per cent had 5 per cent or more. In another series of 62 cases, there was 4 per cent or more in 24.2 per cent of cases, and 5 per cent or more in 12.9 per cent of cases.

Technique.—In a series of 56 patients with the disease, cold agglutinins were never higher than in a dilution of 1:32 [Evans (182)]. Bennett *et al.* (159) recommends repeating the test at frequent intervals if one wishes to avoid missing a significant titer. The variability of the results in the test is blamed by Zarofonetis & Oster on variations in agglutinability of sheep erythrocytes (183). This conclusion is not in accord with my personal experience in a rather large body of serologically studied cases during the last 16 years. I have found the agglutinability of the sheep cells to be quite stable and dependable. Evans (184) tried sodium citrate, heparin, modified Alsever's solution, and defibrination, and found that 2 ml. of a 5 per cent solution of sodium citrate added to 10 ml. of freshly drawn sheep blood was most reliable.

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fever, rheumatoid arthritis, cirrhosis, scleroderma, dermatomyositis, or periarteritis nodosa (190), in subacute bacterial endocarditis, various blood diseases, lymphoma, or carcinoma [Lee *et al.* (194)]. It was demonstrated in pernicious anemia in relapse, dermatitis herpetiformis, chronic discoid lupus erythematosus, chronic disseminated lupus erythematosus, and probably in a case of subacute disseminated lupus erythematosus, in myeloma and leukemia (191). In amyloidosis of the marrow, Lee saw one LE cell, but it was chemically different from true LE cells (194). The phenomenon was observed in at least one case of hemolytic anemia (195). It is for these reasons that Berman chose the presence of 10 LE cells per 500 neutrophils in marrow smears as strong evidence of acute disseminated lupus erythematosus. This arbitrary criterion has not yet been checked on peripheral blood preparations, which technique is now commonly used. Two *in vivo* techniques of demonstrating the LE phenomenon have been reported. In one the skin is abraded and a coverslip applied over some plasma from patients with acute lupus. The coverslip in removed at intervals, and in the preparation typical LE cells can be seen [Rebuck *et al.* (196)]. In another technique a cantharides blister is produced, and the base of the blister curetted A smear made from it may show the characteristic phenomenon [O'Leary & Watson (197)]. The suggestion that the LE cell is an artifact caused by anticoagulants was definitely disproved because it can be demonstrated with difibrinated blood, with blood collected in tubes coated with silicone, and in clotted blood [Eppes & Ludovic (198)]

Technical modifications.—The technique of demonstration has been *variously modified and simplified (195, 199, 200) The phenomenon* can be demonstrated with great regularity in the overwhelming majority of correctly diagnosed cases of disseminated lupus erythematosus. Therefore, one has to assume that reports of low sensitivity of the test may result from lack of familiarity with proper technique [Stich (201)]. Bodies similar to LE cells have been described by Klemperer *et al* in lymph nodes and kidneys in patients with the disease (202). Schleicher described an erythrocyte aggregation factor in the plasma and serum of patients with acute lupus erythematosus (203). The technique of demonstration was promptly modified by Fjelde (204). Red cells mixed with highly concentrated solutions of albumin and kept in the refrigerator are clumped strongly and characteristically. This reaction is not characteristic for lupus erythematosus but was found in a variety of other conditions such as bacterial infections.

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TOXICOLOGY[1]

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The impressive growth of toxicology during the present generation has resulted largely from poisonings in industry which have focused attention on various hazardous types of employment. The rapid development of industry, especially in the field of chemistry, has brought many new substances into commercial being and has necessitated information regarding their toxic qualities. Because of this need for basic information, investigations have been confined for the greater part to acute and chronic toxicity studies However, the by no means neglected field of detoxication mechanisms is receiving increasing attention Much progress is being reported with reference to the effects of many of the metallic poisons, and some insight is being gained regarding their mode of action on tissues and organs as well as on various enzyme systems In contrast to organic substances, very little success is attendant on the part of the organism as a whole in its attempt to detoxify in metal poisoning To some extent this is effected by deposition of these metals in the form of insoluble compounds in various tissues, but in some cases specific enzyme systems are affected or the normal function of certain amino acids is interfered with by combination with the metal. The barrier presented by the intestinal wall, while permitting a selective absorption of necessary nutrients, and the effective function of the liver in rejecting and excreting in the bile undesirable trace metals, all act to protect the organism as a whole from many undesirable elements. However, when inorganic dust or fume is inhaled into the lungs, this normal protective mechanism is ineffective; the foreign material may be carried directly into the circulatory system and severe damage may result.

Inorganic Substances

Arsenic—Arsine, because of its virulence, has claimed many lives, yet, doubtless because it is an industrial poison, has attracted less attention than many other substances The earlier fatalities largely resulted from ballooning operations, where arsenic was present as an impurity either in the metal or the acid used for the generation of hydrogen [Glaister (1)], and thus have been of historical interest only. However, arsine is again achieving importance as an industrial poison Within the past two years 35 cases and 9 deaths have been directly traced to arsine. While some of these have been due to the evolution of arsine from metals or metal containers treated with acid, the

[1] The survey of the literature pertaining to this review was concluded in July, 1951.

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lium oxide into the ear veins of rabbits. In these experiments, osteosarcomas developed in six of nine animals. Aldridge and his associates (15) have succeeded in producing bone sarcomas in rabbits by the intravenous injection of zinc beryllium silicate and beryllium silicate, as well as beryllium metal. According to these investigators, beryllium ions react rapidly with certain tissue proteins, including plasma proteins, and are poisonous to all living cells when brought into intimate contact with them. Barnes (16) states that there no longer is any doubt that beryllium is capable of producing neoplasms in the rabbit Stokinger and his associates (17, 18, 19), in a comprehensive study of beryllium toxicity, determined the acute toxicity of beryllium sulfate mist and in further experiments found that beryllium salts when inhaled as a mist with hydrogen fluoride increased the deposition of fluoride in tooth and bone. In experiments with beryllium oxide, four grades of dust were employed differing in particle size and state of aggregation. Two grades produced injury to the lungs, while the other two grades failed to produce pulmonary damage even with prolonged exposure Following exposure of laboratory animals, it was possible to correlate the acute pneumonitis with particle size. These experiments represent an advance toward establishing permissible maximum concentrations of exposure In an attempt to gain further insight into the mechanism of beryllium toxicity, Grier *et al.* (20) carried out experiments which suggest that beryllium acts as a phosphatase inhibitor while magnesium acts as an activator of phosphatase. Klemperer *et al.* (21) found a partial inhibition of alkaline kidney phosphatase activity by beryllium concentrations of the order of $10^{-6}M$. The treatment for berylliosis based on the use of pituitary adrenocorticotropic hormone (ACTH) and cortisone, which is receiving much attention, has been discussed by Frawley (22) from the point of view of physiological effects and the prevention of complications. With regard to industrial exposure, Titus (23) has shown that the concentration of beryllium in the air during machining operations of beryllium stainless steel can be maintained under a microgram per day by means of proper exhaust ventilation Attention should be drawn to two excellent reviews of the already ponderous subject of beryllium toxicity. Truhaut (24) gives a well rounded discussion and review, while Vorwald (25), in addition to printing the 39 papers of the 1947 Saranac Conference, has given a very complete bibliography of some 684 references

Cadmium—Cadmium oxide fume, which in the past has occasioned marked illness and some deaths, does not apparently have its counterpart in cadmium oxide dust The extensive investigation of Princi & Geever (26) in which 30 dogs were studied for one year has shown that neither cadmium oxide dust nor cadmium sulfide dust produced any observable physiological change in the animals in that time, nor were there any demonstrable pathologic changes produced in the lungs, liver, or kidneys. Further

majority have originated in certain smelting and refining operations. Metallic dross containing arsenides in contact with water, or arsenical compounds in contact with nascent hydrogen, appear to evolve considerable amounts of arsine. Nau (2) reported fourteen cases of poisoning with no deaths from arsine generated in this manner. Spolyar *et al.* (3) and Pinto *et al* (4) reported 13 cases hospitalized and 4 deaths resulting from the wetting of dross and Morse & Setterlind (5) report two deaths from a similar source Spolyar states that freshly formed arsine is odorless and develops its garlic-like odor only after standing for some time. This statement is borne out by the observations of workers who have been exposed to arsine Newly formed arsine is therefore a particularly insidious poison. Among other cases recently reported, that of Steel & Feltham (6) is also of interest because of the rather complete clinical discussion In this case a chemist suffered exposure to arsine while mixing oxalic acid, zinc dust, sulfur, and other material in equipment which had previously contained arsenious oxide. Poisoning was severe, but recovery followed. Dimercaprol (2,3-dimercaptopropanal; BAL) has been recommended for the treatment of arsine poisoning, perhaps because of its successful use in poisoning from organic arsenicals. Assouly & Griffon (7), for instance, used it in treating one of two cases of arsine poisoning arising from acid used to remove a chalky deposit from a metal container. The case treated with BAL recovered. Different results, however, were obtained by Reymond and his associates (8) in treating two cases of arsine poisoning with BAL. Although one of the patients recovered, the BAL was found to be of no value. In fact, it had an adverse effect in provoking vomiting. Furthermore, Pinto *et al.* (4) state that BAL does not stop or prevent the arsine destruction of red cells.

Beryllium.—Beryllium continues to evoke a great deal of interest, and numerous cases of tissue granulomata ascribed to beryllium are currently reported. In some instances, these granulomata have been caused by material traumatically introduced into the skin. Dutra has described five cases of this type (9). Excision of the lesions resulted in a cure in each instance. More recently, Dutra (10) has produced experimental granulomata of the skin by implantation of a beryllium phosphor In another instance, two lots of beryllium oxide powder exhibited differences in severity of reaction depending upon their physical properties, the more intense reaction being produced by the oxide which had been less calcined. The pulmonary type of granulomatosis has, of course, been of more especial interest. Slavin (11), for instance, has reported five cases with one death, and DeNardi and his associates (12) have reported ten cases, to mention but a few of the many reported. Experimentally, Davies & Harding (13) have moved the matter an important step further by producing granulomata in the lungs of rats as a result of beryllium dusting Davies has pointed out that the particle size affects the rate of solution and may be an important factor in producing granulomata Dutra & Largent (14) were able to produce osteosarcomas by injecting beryl-

injected intravenously, acts apparently as a neuromuscular poison. It was found that gallium is deposited in the bones and that the gallium deposited in bone tissue is slowly released after a period of months. This fact has led to the successful therapeutic use of radiogallium Ga^{72} on osteogenic neoplasms.

Lead.—Although lead poisoning continues to be of considerable interest, no significant advance has been made recently in the biochemistry of plumbism itself Education and preventive measures have served to decrease the incidence of poisoning markedly, but it still continues to be a matter of some magnitude owing to the widespread and varied uses of this metal. The majority of the cases of lead poisoning occur in industry, although nonindustrial cases appear from time to time. Reisberman (45), for instance, reported six cases of chronic lead poisoning, three of which died, from lead-contaminated well water. Chiodi & Cardeza (46) have noted the occurrence of hepatic lesions in lead-poisoned animals fed a high-fat diet. Casein and methionine apparently prevent such damage to the liver. Troisi (47) has reported an interesting case of arteritis obliterans in a worker who had suffered 22 years of exposure to lead The essential differences between lead encephalopathy caused by exposure to lead dust and that caused by tetraethyl lead have been pointed out by Hay (48). The stippling of red cells as a diagnostic aid is still usefully employed, and MacFadzean & Davis (49) have thrown some light on the phenomenon of stippling in general and particularly in relation to the anemia of lead poisoning They have made the interesting discovery that a certain proportion of the granules of stippling give a positive reaction for iron. A modification of McCord's basophilic aggregation test has been proposed by Larsson & Swenson (50) in which toluidine blue or methylene blue dye are used at a pH of between five and six. Toluidine blue, which stains more intensely, is the more suitable for practical use. According to Schiøtz (51), the basophilic aggregation test is faster and easier to apply than the stippled cell count but fails in a number of cases; the latter method remains official in Norway Although little attention has been paid in this country to nephritis in connection with plumbism, three cases of chronic nephritis following exposure to lead have been reported recently by Gsell (52). Lane (53) has emphasized the importance of considering renal disease following prolonged exposure to lead Several investigations involving the use of BAL have been made in the treatment of lead poisoning. In acute lead poisoning Bastrup-Madsen (54) found that urinary lead was increased considerably immediately after commencing dimercaptopropanol therapy Ginsburg (55) injected BAL intramuscularly in rabbits shortly following the administration of lead acetate This was found definitely to increase the excretion of lead in the bile Anderson (56) objects to the proposed BAL therapy for lead poisoning, however, stating that the BAL-lead complex is twice as toxic as lead and that BAL does not produce appreciable deleading in spite of the initial but transitory increase in urinary lead output There is still some doubt

studies with the oral administration of cadmium sulfide and cadmium sulfoselenide, using rats for experimental animals. No observable damage was apparent, and the only effect noted was a slight taste aversion when the diet contained 1 per cent or more of the pigment. However, Friberg (28) has noted the occurrence of proteinuria among workers exposed to cadmium dust and is inclined to attribute this proteinuria to cadmium. The distribution of cadmium in the tissues following inhalation has been investigated by Potts *et al.* (29) using cadmium 115 as a tracer. The importance of studying the blood chemistry following cadmium poisoning is stressed by Cotter & Cotter (30). Very fine particulate cadmium oxide dust is practically invisible in lung sections under the microscope As demonstrated by Thiers and his associates (31), the particles may be revealed by subjecting unfixed sections of lung tissue to the vapor of 8-hydroxyquinoline, which converts the particulate oxide to cadmium 8-hydroxyquinolinate dihydrate The latter shows an intense green fluorescence under ultraviolet light

Fluorine.—It is recognized that exposure to excessive amounts of fluorides is inimical to health, but industrial exposures of this type are generally well controlled. Truhaut (32) has pointed out the difference between industrial and spontaneous fluorosis. The latter occurs where the soil or the drinking water is rich in fluorine. A peculiar disease of domestic animals and man called "dermeus" has been observed in French Morocco as well as in other parts of North Africa and is characterized by a complex dystrophy of the secondary dentition. This has been attributed to the use of water rich in calcium fluoride. Kilborn *et al.* (33) have also discovered an endemic center of fluoride poisoning in Southwestern China. In this case the toxicity of the drinking water produced a disabling arthritis and spondylitis. According to Miller (34), the ingestion of 10 mg. of nonacid fluorides per day is harmless in man McClure's recent experiments (35) indicated that fluorine may be administered in water in the form of sodium fluosilicate with apparently the same effects on teeth as when sodium fluoride is used. The popular interest in fluoride therapy with reference to tooth decay is increasing, and many localities have requested the fluoridization of the municipal drinking water supply. No experimental work has been reported at these low concentrations regarding the well-known powerful inhibition of fluorides on enzyme reaction, specifically glycolysis, and the possible effects of this inhibition on human metabolism. However, Black and his associates (36) administered as much as 320 mg. of sodium fluoride per day to human subjects for five or six months without evidence of acute or chronic toxicity. Badger (37) states that the level of fluorine should be maintained at no more than 0 7 p p m in the drinking water to prevent defects in the permanent teeth of children.

Gallium—Pioneer work on the toxicology of gallium was undertaken by Dudley and his associates (38 to 44) and has resulted in an interesting therapeutic application of radiogallium Gallium lactate, which has an LD_{50} value of 46 mg. Ga/kg for rats and 43 mg Ga/kg. for rabbits when

Agene.—For a number of years, the bleaching of whole wheat flour has been carried out by employing nitrogen trichloride, or the so-called agene process. It has been shown that the feeding of flour treated in this manner to several different species of animals, i e., dogs and rabbits, leads to the production of convulsive disorders. In the dog the physical characteristics, the electroencephalogram findings, and a number of biochemical changes in the blood observed after "agene" intoxication are similar to the findings in human cases of grand mal epilepsy. In addition to the above there has been observed to be a dysfunction of the adrenal cortex in agene intoxication. The work of several investigators has led to the general conclusion that the toxic material is altered methionine, a compound which appears to be identical with the toxic factor isolated from nitrogen trichloride-treated flour This substance has been synthesized and has been called methionine sulfoximine. Experiments in which humans were given fairly large quantities of agenized material indicate that the human is rather insensitive to this material [Bonnycastle (66)].

Rare earths—Very little toxicological interest has been attached to the rare earth metals, primarily perhaps owing to their minor utilitarian importance, but also because what information has accumulated has shown them to be of little physiological importance Recently, however, Cochran (67) and his associates have included certain of these in their investigation of lanthanum, tantalum, strontium, columbium, yttrium, and cesium. The oral toxicities of tantalum, lanthanum, and zirconium were found to be very low Yttrium was found to be relatively nontoxic, and cesium has a very low intraperitoneal toxicity. Columbium, both as potassium columbate and columbium chloride, was quite toxic to rats when administered intraperitoneally. Experiments with succinic dehydrogenase revealed that lanthanum and aluminum show similar biologic properties towards this enzyme, and most of the other metals tested showed inhibitory effects with adenosine triphosphate. Columbium showed the most pronounced inhibitory effect, which is of interest as it proved to be the most toxic of this group of metals. McClinton & Schubert (68) found that animals survive relatively large doses of the citrate and gluconate salts of zirconium and of the citrate of thorium. Cerium does not affect either the blood picture or the growth of animals, and, in general, has a low toxicity rating [Meyer (69)].

Silicon—The fundamental nature of the toxic action of silicon dioxide remains as inscrutable or seemingly as distant as ever. In fact, the accumulation of scientific data appears to have widened the gap rather than otherwise. Although the popular flurry of interest in silicosis has diminished, numerous earnest workers have kept the [illegible]

on the basic problem of silicosis. The more fundamental information is to be obtained only from silica itself and the physiological response which it evokes.

in general among the more conservative-minded investigators regarding the use of BAL as a therapeutic agent in lead poisoning. Porphyrinuria in lead poisoning has been a matter of interest to investigators of lead poisoning for the past 60 years. It is rediscovered from time to time and presented with additional embellishments as an index of either lead absorption or of lead poisoning. However, as Maloof (57) and others have pointed out, porphyrinuria is seen in many illnesses and is not specific for lead absorption nor for lead intoxication. While Salomon & Cowgill (58) find increased amounts of coproporphyrin in dogs after lead injection, they point out that the great sensitivity of dogs to lead is not reflected in their porphyrin metabolism and that it is a late, rather than an early, sign of lead exposure. Waldman & Seideman (59) propose the semiquantitative porphyrin test of urine as a screening test for lead absorption in places where large numbers of workers are exposed to lead. Of itself, porphyrinuria is not diagnostic, according to McCord (60), but as a screening procedure among lead-exposed workers, otherwise healthy, it may be applied as a measure contributory to diagnosis

Mercury.—The many and diverse uses of mercury and the insidious nature of its effects following chronic exposure constitute it a hazard of some magnitude, although the actual number of cases of poisoning may not be great. Vigliani & Baldi (61) have reported 100 cases of mercury poisoning occurring over a period of years in a single felt hat factory in Italy. When the use of mercury in the felt hat industry in this country was still legal, the majority of cases of mercurialism also occurred in that industry. However, isolated uses of mercury still exist in many industries, and the number of individuals potentially exposed is substantial The extent of exposure, of course, varies with the nature of the operation, and poisoning of the mercury worker is almost exclusively a result of mercury dust, fume, or gas absorbed through the respiratory tract In one industrial operation (assembling of mercury primers), Ledergerber (62) found workers breathing in an estimated 4.2 mg. of mercury per day and estimated the retention at 1.3 mg. per day. The absorption at this level was confirmed by the urinary findings of mercury as high as 1 mg. per l. An interesting instance of mercury exposure has occurred among policemen [Agate & Buckell (63)] who use "gray powder"—a mixture of chalk and mercury—for the detection of finger prints as this mixture produces a particularly good image for photographing. Evidence of mercurialism was found in about 22 per cent of those using this material Organic mercurials, such as the phenyl derivatives used chiefly as fungicides for the treatment of seeds, are potentially dangerous in manufacture, storage, and handling. Phenyl mercuric acetate has been shown to be chronically more toxic to the rat than mercuric acetate (64) and causes 10 to 20 times as much storage of mercury in the liver and kidney as the latter Renal damage was found to be particularly severe leading to large, fibrous, granular kidneys BAL has been recommended for the treatment of mercury poisoning (65) and was recently shown to be effective in two instances

These areas were denser than those seen in silicosis. There was no evidence of systemic damage, and the pseudo-nodulation was classed as benign, nonspecific pneumoconiosis. Dundon & Hughes (82) report a case in which there had been no respiratory symptoms, but in which stannic oxide particles had accumulated in the regions of perivascular, peribronchial, and subpleural lymphatics, producing sharp shadows. The shadows were not cast by foci of fibrous tissue, and the tin oxide thus deposited is systemically nontoxic. Similar cases of benign pneumoconiosis arising from exposure to tin oxide are reported by Bartak *et al* (83) and by Cutter *et al.* (84).

Carbon Compounds

Organic substances, although generally lacking the precision of determination in minute amounts that the majority of the inorganic substances possess, have nonetheless many compensatory advantages for the investigator which permit him to observe their progress through and transformations in the body. Furthermore, with the present day technique of using labelled elements, many organic substances can be determined as readily and in as small amounts as the inorganic substances By far the majority of industrial organic substances of toxicological interest fall within the general group of halogenated hydrocarbons or within the groups of nitro and amino derivatives. The former includes a large group of currently applied insecticides Injuries in the halogenated hydrocarbon group have generally resulted from exposure by inhalation. The attempt to review even a fraction of the literature devoted to the toxicology of the synthetic organic compounds would be impossible in this section It would appear to be more pertinent, therefore, to present certain relationships which many substances have in common and to confine the discussion to selected substances

Benzene—It has long been recognized that the aromatic hydrocarbons cause a pronounced physiological response, whereas the aliphatic hydrocarbons—at least in the lower series—are physiologically inert. Benzene has claimed more lives in industry than any other hydrocarbon It is widely used, but its toxic properties are frequently not sufficiently appreciated. One of the chief effects of exposure to benzene vapor is a characteristic form of anemia Both Vigliani & Saita (85) and Sacca (86) have also pointed out a syndrome clinically typical of myelogenous leukemia Troisi & Amorati (87) found anemia in 38 out of 40 cases of occupational benzene poisoning. A case of erythro-leukemic type of anemia resulting from benzene poisoning has recently been described by Galavotti & Troisi (88) Folic acid has been applied as treatment in rabbits poisoned with benzene, but, while increasing the leucocytes, it did not affect the erythrocytes [Marsico & Polosa (89)]. Ascorbic acid introduced intramuscularly in benzene poisoned rabbits has been shown by Pecora (90) to increase the excretion of conjugated sulfates A study of the bone marrow by Dietz & Steinberg (91) of benzene-poisoned rabbits showed that the action of benzene caused an increase in water content

Not all types of silica produce the same effect. Recently, King (70) has found that granite dust—a mixture of quartz, feldspar, and mica—when injected intratracheally in suspension into the lungs of rats induces only a mild reticulin reaction not to be compared with the silicosis produced by pure quartz Silverman & Moritz (71) found that the toxicity varies with the surface area of the silica particle. Unfused quartz is more reactive than the fused material. The materials used were of similar particle size, 1.7 to 1.8 μ. Spiculate particles having a large surface area in relation to mass evoke a significantly greater tissue reaction than do spherules of comparable size and identical composition. The theory first proposed by Heffernan (72) that only freshly fractured silica is biologically active has been vigorously criticized by Wright (73), who has attacked the various hypotheses on which this theory is based. Comparative animal experiments cited by Rüttner (74) also have demonstrated that pure, recently fractured quartz is no more active than "old" quartz. Vigliani *et al.* (75) have shown that measurement of the globulins in the blood serum can assist in both the diagnosis and the prognosis is cases of silicosis The application of the electron microscope to the examination of particulate quartz obtained from the lungs of workers has revealed a process of disintegration according to Beintker & Meldau (76). These investigators state that the disintegration of the particle is revealed in the form of very minute droplets on the surface of the particle and that these droplets appear to be silicic acid in colloidal form. It is thought that this colloidal material may play an essential role in initiating silicosis.

Asbestos.—Asbestosis has been officially recognized as an industrial disease since 1930, yet the exact mode of action of asbestos is still obscure. The fibrogenic action differs from that of silica in that the effects are produced only by long asbestos fibers while the very short asbestos fibers appear to have little or no effect. The long fibers apparently block the finer bronchioles and produce fibrotic changes as a result of irritation According to Vorwald (77), the mode of action of the long asbestos fiber is primarily mechanical rather than chemical in nature. In a recent study of 40 cases of asbestosis at necropsy, Lynch & Cannon (78) found support for the belief that fibrosis does not progress indefinitely after cessation of exposure Cartier (79) has found cases of asbestosis only in those employed for at least 14 years and exposed to air containing at least 5 million fibrous particles per cubic foot varying in length from 10 to 250 μ. According to Hueper (80), asbestos has been suspected, but not yet proved, to be a cause of lung cancer

Tin.—Tin is one of the most innocuous of metals from the standpoint of ingested material. Large amounts are commonly consumed in canned foods to which it does not impart any taste, flavor, or physiological effects It is therefore of interest to note that tin oxide has recently been implicated as a source of pneumoconiosis. The first case of this type was reported by Pendergrass & Pryde (81) The reoentgenogram of an individual whose occupation was that of bagging tin oxide showed discrete densities throughout both lungs

from the blood stream with extreme rapidity [Sperling (101)] Methyl bromide is responsible for occasional deaths arising from exposure to the vapor from using or emptying fire extinguishers containing this substance or from its use in fumigation Gayral (102) has pointed out the severe vasodilating action of methyl bromide Buckell (103) finds that methyl iodide is at least as toxic as methyl bromide and about 10 times as toxic as carbon tetrachloride Injuries to health following exposure to trichloroethylene have been pointed out by Alexander (104). The vapor of tetrachloroethane has a toxic action similar to chloroform but is about four times as potent 1,1,1-Trichloroethene has recently been investigated by Adams and his associates (105), who found minor organic injury consisting of fatty changes and some necrosis of the liver only when exposure was severe. It is suggested that considerably greater concentrations of this compound can be tolerated by man than such substances as trichloroethylene and tetrachloroethylene—similar in magnitude, in fact, to that of dichloromethane. The impression has rather generally prevailed that trichloroethylene is relatively innocuous. However, Cotter (106) has recently described 10 cases of severe poisoning from this material. [illegible]

sis. A relationship has been established between the excretion of trichlorocetic acid and known atmospheric concentrations of trichloroethylene This information will be of importance in estimating exposure in industrial cases

Amino and nitro derivatives—The war-initiated investigations concerning such substances as trinitrotoluene, tetranitromethylaniline, and cyclotrimethylenetrinitramine have added much information concerning human exposure to these substances While the LD_{50} was found by von Oettingen and his associates (108) to be rather high for cyclotrimethylenetrinitramine, much smaller amounts administered to rats caused hyperirritability and convulsions. This is of particular interest in view of epileptiform attacks experienced by workers handling the dry material, noted by Barsotti & Crotti (109) during the war Trinitrotoluene poisoning has occasioned much interest and many animal studies have been made to find the mode of action of this substance. Progress has been made in elucidating the metabolism of this substance, but not all the metabolites have been identified nor are all the physiological effects clearly set forth. Pecora (110) found a 50 per cent decrease in the total protein in the plasma of TNT-poisoned rabbits, chiefly in the albumin fraction, while DiLauro & Sessa (111) found degenerative changes in the liver, kidneys, and spleen in chronically poisoned rabbits, changes which were not so apparent in animals protected with liver extract, B complex, or methionine The dyestuff industry affords many instances of poisoning, chiefly from the intermediates other than aniline, although cases of poisoning from the latter are reported from time to time—chiefly resulting from splashing the material on the skin. According to Jasin-

and a decrease in lipids, total and nonprotein nitrogen, and the nonsulfur fractions. When both vitamin C and rutin are used together, the ascorbic acid has a definite protective effect and causes longer survival, while rutin has a specific effect on the capillary wall and reduces capillary fragility [Pecora (92)]. Srbova *et al* (93) have made a systematic study of benzene poisoning in man. Benzene concentrations in inhaled and exhaled air and in blood and urine were measured in 23 subjects who inhaled benzene vapor in concentrations of 47 to 110 p p.m The rate of absorption is highest in the first few minutes and then quickly drops to about 50 per cent. The amounts eliminated by the lungs and the kidneys and the amount remaining in the body undergoing metabolism could be determined and the time necessary for elimination from the body could be calculated. In their studies on the metabolism of benzene, Porteous & Williams (94) isolated for the first time as metabolites of this substance, two additional phenols—quinol and hydroxyquinol. The conjugated products with glucuronic and sulfuric acid are nontoxic. Since protein is the main source of sulfur, an adequate supply appears to be necessary to maintain the normal function of the liver for the detoxication of the phenols.

Halogenated methanes.—The relation between chemical composition and toxicological action has long been of interest to investigators in the field of carbon derivatives. Von Oettingen and his associates (95) have evaluated the various types of physiological response to the chlorinated methanes by studies of the acute toxity of mono-, di-, tri-, and tetra-chloromethane in mice and of their effect in equimolecular and equitoxic concentrations in dogs. With the exception of monochloromethane, it was found that the various physiological functions fundamentally follow their physicochemical properties Because of the availability, wide use, and toxic properties of this substance, it is not surprising that deaths from exposure to carbon tetrachloride continue to be reported annually In many instances, the fatal cases are associated with acute or chronic alcoholism Poisoning is usually characterized by hypochloremia and alkalosis [Germain & Andre (96)] and hepatic and renal changes Moon (97) has discussed the pathology of 12 fatal cases of carbon tetrachloride poisoning He found that the hepatic lesions were characterized by early severe central necrosis of the lobules followed by an inflammatory reaction. The renal lesions in the later stages were characterized by profound tubular degeneration. In treating patients following exposure to carbon tetrachloride, Gugua & Scudder (98) emphasize therapy aimed at combating acidosis, low calcium, and low potassium Experimentally, Campbell & Kosterlitz (99) found that a diet rich in carbohydrates and poor in fat and protein gives the greatest protection against liver injury if given for short periods prior to the administration of carbon tetrachloride However, prolonged protein deficiency renders the liver highly susceptible to this type of injury. BAL therapy has been found to be ineffective in carbon tetrachloride poisoning (100) Methyl chloride administered intravenously disappears

Carbon disulfide.—Despite the fact that the unique toxicity of carbon disulfide, which is used extensively in the viscose silk industry, is well known, acute and fatal cases of carbon disulfide poisoning continue to be reported. For instance, Gordon (123) reported that three men, one of whom died, were overcome from the fumigation of 12,500 bushels of wheat with 40 gallons of carbon disulfide. A comprehensive study by Brieger and his associates (124 to 127) has disclosed new information concerning the effects of carbon disulfide on tissue respiration, glycolysis, the digestive enzymes, the blood cells and bone marrow, and the heart. While there was some indication of an inhibitory effect on tissue respiration with carbon disulfide, it was found to be without influence on the activity of lipase, pepsin, and trypsin. Extended exposure to approximately 300 p.p.m. of carbon disulfide produced a statistically significant pseudo-eosinophilia with a corresponding decrease in lymphocytes. Neither electrocardiograms nor histological examination of the heart revealed any significant changes in exposed animals. A study of the metabolism of carbon disulfide indicates that rather large amounts of this substance are converted to other organic sulfur compounds and particularly to inorganic sulfate. Strittmatter *et al.* (128) used labeled carbon disulfide (S^{35}) to follow these metabolic changes. Intracardially injected labeled carbon disulfide is characterized by marked retention in the tissues, by its slow release, and by the extent to which the organism metabolizes the retained CS_2^{35} and effects its excretion in the urine—largely as inorganic sulfates. Vigliani (129) proposes a level of 0.15 mg. of CS_2 per l. as the maximal allowable concentration of carbon disulfide in industry.

Insecticides.—Insecticidal studies have reached such a volume that to attempt even to enumerate them would be beyond the scope of this discussion. Various centers, notably the Communicable Disease Center of the Public Health Service, have contributed substantially to knowledge in this field. Furthermore, the important insecticide of today is frequently of minor importance tomorrow. DDT, although still important, has been replaced in many instances by other substances. One of these substances, chlordan, is less acutely toxic to rats than DDT, but its chronic toxicity is considerably greater [Stohlman *et al.* (130)]. The extent to which DDT is being used and distributed is indicated by the work of Laug *et al.* (131), who examined 75 samples of human fat and 32 samples of human milk of individuals not otherwise exposed to DDT than through their diet. As high as 34 p.p.m. were found in human fat and 0.77 p.p.m. in human milk. Princi & Spurbeck (132) have made a study of 24 men engaged in the manufacture of chlordan, aldrin, and dieldrin, who were exposed to an average concentration of 5 mg. per m^3 of air for periods of from one to three years. No evidence of any deleterious effects on the respiratory system, the nervous system, the liver, kidneys, or the hematopoietic system of any of these individuals was noted. The organic phosphorus insecticides are by far the most dangerous in use so far. Eight deaths have occurred in the formulation or use of *o,o*-diethyl-*o*-*p*-nitrophenylthiophosphate (parathion), and 88 claims for compensation have

ski (112), methemoglobin is not found in the blood serum in the acute phase of aniline poisoning but occurs in the hemolysed blood. Angeleri (113) has found the methemoglobin values for blood to be doubled or even quadrupled in workers handling amino or nitro derivatives of benzene, without causing cyanosis or other objective or subjective symptoms. Lyons (114) found cases of hematuria among aniline workers which was finally traced to contact with 5-chloro-*o*-toluidine. Detoxification studies have been made by Smith & Williams (115) with respect to aniline which indicate that about 28 per cent of the aniline administered to rabbits by mouth is excreted as ethereal sulfates of *o*- and *p*-aminophenol and 4-aminoresorcinol and that about 70 per cent is excreted as glucuronides. In connection with the controversial situation with regard to aniline as a cause of bladder tumors, it should be mentioned that Ekman & Strombeck (116) have produced keratosis and proliferation of the bladder to the point of papilloma formation by adding 0.1 per cent of aniline to the basic diet of white rats. Xylidine has occasioned some interest because of its possible use as a substitute for lead tetraethyl in gasoline. In their extensive study of monomethylaniline and xylidine, Treon and his associates (117, 118) found that both these substances possess a high order of toxicity and have somewhat similar physiologic effects. A cautious estimate of possible safe limits of human exposure was made of concentrations of the order of five parts of xylidine or two parts of monomethylaniline per million of air, provided that careful medical supervision was instituted.

Meigs and his associates (119) have studied the metabolites formed by exposure to 4,4′-diaminodiphenyl (benzidine) both in animals and in man. It appears that, while the urinary excretion of benzidine itself amounts to only 2 to 6 per cent, substantial amounts of benzidine diorthoglucuronide and benzidine diorthoethereal sulfate are formed and excreted in the urine.

Compared with the aromatic amines, the aliphatic amines are of little physiological interest, and it is only recently that any study of their toxicity has been made. Nonetheless, they are industrially important and Brieger & Hodes (120) have made an investigation of monoethylamine, diethylamine, and triethylamine by exposing rabbits to the vapors of these substances and noting their physiological response. Histological examination following exposure revealed pulmonary irritation and multiple corneal erosions and edema in concentrations as low as 50 p.p.m. There was no uniform difference in degree between the three amines studied.

Silicones.—The organosilicon oxide polymers usually referred to as "silicones" have recently achieved some commercial importance. One of these substances, methylpolysiloxane, is used to suppress or prevent foam in a number of food products, and it is therefore important that its toxicity rating should be negligible. Rowe and his associates (121, 122) have recently completed a long-term study of the toxicity of methylpolysiloxane using laboratory animals. Extending over two years, this study failed to reveal any significant effects from feeding this substance. As a class, the methyl and mixed methyl and phenylpolysiloxanes appear to be low in toxicity.

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NEOPLASTIC DISEASES[1,2]

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Introduction

In no field of medicine is early and correct diagnosis, experience, knowledge, and the proper evaluation of multiple, and often conflicting, factors more important than in the neoplastic diseases. The course of cancer is progressive, and the proper treatment will vary with the type of cancer, the extent of the disease, the general condition of the patient, and the quality of the medical facilities. The clinical dilemmas and problems presented by cancer have been reviewed, debated, analyzed, and, sometimes, clarified in the enormous literature that appears yearly on the subject. In the absence, in most cases, of any simple method of curing or controlling the disease, the elaborate recording of experience may serve to improve the management of the individual patient.

The natural course of cancer—its peculiarities and variations—is under close scrutiny. The beautifully written papers of Nicholson (1), on the natural evolution of cancer, collected under the title, *Studies on Tumor Formation*, merit the attention of all workers in the cancer field. The survival time of untreated patients with cancer has been summarized from the literature with additional data by Shimkin (2). MacDonald (3) has emphasized the importance of "biological predeterminism" in the course of cancer and its response to treatment; this factor carried greater weight than early diagnosis in the survival rates of patients with cancer of the breast, stomach, or colon, and with osteogenic sarcoma, and only in carcinoma of the cervix did the survival rate increase definitely with early diagnosis Park & Lees (4) independently reached approximately the same conclusion in regard to breast cancer, concluding that treated patients had not been clearly shown to have a substantially higher five-year survival rate than untreated cases. Presumably, however, the treated patients alive at five years have a good chance of being free of cancer. These reports may seem pessimistic and somewhat fatalistic, but they do not question the value of early diagnosis and adequate destruction of the cancer as the foundations of curative therapy They are examples of the necessary and continuing critical assessment of the present methods of treatment

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was 42 per cent. The proper surgical treatment of cervical cancer is radical hysterectomy with pelvic node dissection (19, 20); while surgery as the primary treatment of cervical cancer is under intensive study and not recommended as yet, it is clearly indicated in radiation failures (21). In far-advanced pelvic cancer, radical surgery offers the only real possibility of cure. In the report of Brunschwig & Pierce (22) on their first 100 cases treated by partial and complete pelvic evisceration for widespread pelvic cancer, 20 were operative deaths, 49 lived one to eight months, nine survived one to two years with considerable improvement but with evidence of disease, and 12 have survived at least 18 months without demonstrable recurrent disease. Ten patients had not gone long enough to permit classification.

In about 50 per cent of the cases of carcinoma of the cervix the disease remains within the pelvis, and in Aldridge & Mason's series (23), 40 per cent of their patients died of uremia resulting from ureteral obstruction; they recommended early diversion of the urinary stream for palliation in the absence of radical surgery. The use of hormonal therapy has not been promising Hertz (24) obtained some degree of interruption with the use of progesterone in 11 of 17 cases, but he does not believe it is a practical method of treatment Freed (25) observed regression of pulmonary metastases in a single case of carcinoma of the fundus treated with androgens, but Miller (26) found no benefit from androgen therapy in 91 cases of various genital cancer. Thirty-three cases of sarcoma of the fundus were reviewed by Finn (27); he recommended surgery, and 21 per cent of his patients have survived 5 to 17 years. Brack & Farber (28) have reviewed the literature on carcinoma of the urethra and added 10 new cases; they advised surgical excision followed by radiation therapy

Breast Cancer

The milk factor is a causative factor in breast cancer in mice, and attempts have been made to demonstrate such a factor in man. Berner's (29) review of the evidence in favor of a milk factor in man is persuasive but unconvincing Prognostic factors in breast cancer have been analyzed by Bloom (30, 31). The histological grade and clinical stage of the disease should be considered in prognosis, and he suggested that differences in the results of comparable forms of therapy may be eliminated by a more precise classification of the stage of disease in each patient. Chris (32) has described the clinical course of 20 cases of inflammatory carcinoma, and feels that therapy has had no effect on survival The indications for surgery in breast cancer have been discussed by Portmann (33); Haagensen & Stout (34), using their criteria of operability, reported a five-year survival of operated patients during the period of 1935–42 of approximately 62 8 per cent, of which 51 3 per cent were clinical five-year cures. Of all patients seen, their over-all five-year cure rate was 38.6 per cent. McWhirter (35) made the highly controversial recommendation that simple mastectomy followed by postoperative radiotherapy is the preferred treatment, and he reported an over-all five-year

The principal task of this review will be to cover the clinical literature on cancer during the past year. It is obviously impossible to present all of this material, and representative papers will be cited that seem to show the present status and the current trends in the management of the various types of cancer.

Uterine Cancer

Evidence is accumulating which suggests that carcinoma of the cervix may be associated with environmental factors. Lombard & Potter (5) stated,

> The strong correlations that exist between cancer of the cervix and marriage before the age of 20, individuals divorced or separated at any time, unrepaired lacerations, last child born to women before age 25, and syphilis indicates that these variables are of etiological significance.

These factors may all be reflections of poor living conditions and personal hygiene. Weiner, Burke & Goldberger (6) re-emphasized the low incidence of cervical cancer in Jewish women, and this disease was not found in 13,000 nuns examined by Gagnon (7), although 12 cases of fundal cancer were diagnosed Dockerty & Mussey (8) presented 16 cases of uterine carcinoma associated with functioning ovarian tumors The natural course and spread of carcinoma of the cervix has been analyzed by Twombly & di Palma (9).

Cytological studies have been useful in suggesting neoplastic changes in the cervix, but the results have not been as good in cancer of the fundus (10, 11). An adequate biopsy of the abnormal appearing cervix is the fundamental method of detecting early cancer (12), and endometrial biopsy with the Novak curette is the most useful method of diagnosing carcinoma of the fundus (13), and a dilatation and curettage is indicated if the biopsy is not diagnostic. "Carcinoma-in-situ" or intraepithelial cancer, an important early form of cervical cancer, must be diagnosed with considerable care. In discussing this problem, Douglas & Studdiford (14) stated that "the cell smear . . . is not a method of diagnosis, but a means to select patients for careful study by biopsy and curettage." Novak & Galvin (15) further indicated the difficulty in diagnosing intraepithelial cancer by presenting 25 cases in whom a diagnosis was made by biopsy, but cancer could not be found in the surgical specimen They recommended sharp conization of the cervix to establish the diagnosis

The comparative value of surgery and radiation therapy in cervical cancer is the subject of many analyses. Schmidt (16) showed, in a small series of cases, that the results of radiotherapy were superior to simple panhysterectomy Hoge (17), in a survey by questionnaire of medical schools in the United States and Canada, found that radiation was the preferred method of treatment. Using the Stockholm technique of radiotherapy, Kottmeier (18) has the following percentages of patients (staged according to the League of Nations Classification) alive and free of disease five years after treatment; Stage I, 71 per cent; Stage II, 50.5 per cent, Stage III, 25.0 per cent; and Stage IV, 11.5 per cent. His over-all five-year cure rate

group as compared to the group in which surgery was available, if indicated. The curative value of total pneumonectomy versus lobectomy is under discussion, with the lesser disability following lobectomy an important factor (42). Cahan *et al.* (57), however, have suggested the use of radical pneumonectomy in suitable cases Seiler *et al.* (58) confirmed the desirability of excising solitary, metastatic lesions of the lung, where the primary has been removed and no other evidences of metastases are found. Of 62 patients in their series, 23 are well and nine have survived three years to date The palliative value of nitrogen mustard in inoperable lung cancer, given alone (59) or in combination with radiation therapy (60), has been demonstrated; in the latter study, a review of the literature revealed a favorable response in

Terminal bronchiolar or "alveolar cell" carcinoma is being diagnosed with increasing frequency. Griffith *et al.* (62) reviewed 51 cases from the literature and added seven new ones. Watson & Smith (63) described 33 new cases, the majority of which were diagnosed in the past two years. They found that cytologic examination of the sputum was frequently diagnostic, the only effective treatment was surgery, and 10 of 16 patients treated by pulmonary resection were alive at two months to five years or longer after operation.

Genitourinary Cancer

Prostatic cancer.—Cytologic examination may be of diagnostic value in the majority of cases (64, 65), but it appears to be positive chiefly when the disease is well established and the patient has not received hormone therapy. An elevated serum acid phosphatase indicates metastatic disease even if roentgenographic evidence of metastasis is not present Patients with an elevated serum acid phosphatase have a poorer prognosis than do the patients in the same situation with a normal acid phosphatase Furthermore, patients with normal acid phosphatase do as well, if not better, on hormonal therapy than the patients with the elevated acid phosphatase (66) Reynolds *et al* (67) managed 104 cases with estrogen therapy and transurethral resection as indicated, and 81 patients have survived an average of 34 7 months thus far, and 22 have lived longer than five years. Hand (68) reviewed 109 cases, and concluded that transurethral resection, or prostatectomy, and early castration and estrogen therapy are the best methods of managing the disease. Harrison & Poutasse (69) have obtained their most satisfactory results in inoperable cases by a combination of orchidectomy and estrogen therapy Conservative management may control the disease for long periods, but it is questionable as to whether the patient is ever cured. Radical perineal prostatectomy in suitable cases (about 10 per cent of patients with clinical evidence of disease) may be curative, and Smith (70) has reported apparent cures in about 50 per cent of the patients selected for the radical procedure.

Okie *et al.* (71) found the implantation of 50-mg. pellets of α-estradiol

survival of 50.5 per cent in all cases except those showing distant metastases when first seen. Among patients deemed operable when first seen, 62 per cent were alive at five years.

In inoperable breast cancer the palliative effect of radiotherapy and hormonal therapy are under intensive examination. Among others, Segaloff *et al.* (36), Nathanson (37), and Stoll (38) have reviewed their experiences, and a report on the current status of hormonal therapy in advanced mammary cancer has been completed by the Council on Pharmacy and Chemistry of the American Medical Association (39). Garland *et al.* (40) have compared the effects of x-ray and hormonal therapy on osseous metastases; they concluded that 70 per cent of the patients with bony metastases are relieved by x-ray therapy, the relief lasted from 50 to 100 per cent of the survival time in three-fourths of their cases, and the average survival was 12 months from the onset of therapy. Steroid hormone therapy in their series relieved pain in 40 to 75 per cent of the patients, and the improvement was of shorter duration than that following x-ray therapy, and the average survival time from the onset of therapy was 8.8 months. It is evident, however, that both hormonal and radiation therapy have a place in the palliation of inoperable breast cancer. Hypercalcemia was a complication in 10 of 71 patients with osteolytic bone lesions, and these patients were temporarily relieved by increased fluid intake and a low calcium diet (41).

Lung Cancer

There appears to be a real increase in the incidence of lung cancer (42, 43). Tobacco smoking has been implicated seriously as a causative factor (42, 44, 45, 46), and a progressive rise in the number of patients with lung cancer is predicted by Korteweg (47).

Of 536,012 chest roentgenograms taken in a mass survey reported by Scamman (48), 398 were suggestive of cancer, and 76 were found to be cancer, an incidence of 14.2 per 100,000 cases. Forty-three of the cancers were presumably primary in the lung. Watson *et al.* (49) have described 46 cancers in 113 lung tumors detected by routine examinations. Hypertrophic osteoarthropathy (50) and diabetes insipidus caused by cerebral metastases (51) sometimes are early signs of lung cancer. Cytologic examination of the sputum and bronchial secretions has become an important diagnostic technique; when searched for by repeated examinations, positive diagnoses may be obtained in 70 to 90 per cent of lung cancers (52, 53, 54).

The five-year survival rate in lung cancer remains disappointingly low. In 362 cases of bronchogenic carcinoma reported by Paulson & Shaw (55), exploration was performed in 182; 107 were resected, but in only half this group was there any hope of cure. In anaplastic or oat-cell carcinoma, which may include 20 to 50 per cent of the cases of lung cancer, operable cases are extremely rare. Buchberg *et al.* (56), in a review of the end results of untreated and treated cases of lung cancer, come to the provocative conclusion that the five-year survival rate was actually higher in the untreated

The increasing use of total gastrectomy has been recommended by Lahey & Marshall (87), and a radical gastrectomy procedure has been described by McNeer *et al.* (88) in selected cases in the hope of increasing the present low cure rate in gastric cancer. Harvey *et al.* (89) has reported a 43 per cent resectability rate in gastric cancer of which 32 per cent were carried out in the hope of cure The best five-year survival figure is about 8 per cent of all patients presenting with the disease, and 25 per cent of those resected in the hope of cure. Lawton *et al* (90) reviewed 1,004 cases seen at the Hines Veterans' Administration Hospital during 1931 to 1947. About 25 per cent of the patients were suitable for resection, and, in a group of 740 cases followed, the five-year over-all survival of proved cases was 7 4 per cent, and 16 per cent of their resected patients were surviving at five years. They believe that gastric analysis, examination of the stool for occult blood, and x-ray examination of the stomach are the most important practical diagnostic procedures. Brain & Stammers (91) reviewed the clinical and metabolic complications in 35 cases following radical gastrectomy; they noted weight loss, low capacity for food, severe "dumping syndrome" in six cases, poor intestinal absorption of fat and steatorrhea, macrocytosis without anemia in 11 cases, no evidence of iron deficiency anemia, and vitamin B deficiency in nine cases. Radiation therapy in esophageal cancer produced marked palliation and prolongation of life, and 8 of 88 patients treated by the rotation technique with tumor doses of 6,500 to 6,800 r delivered in 35 to 40 days were apparently free of disease three or more years after treatment (92).

Lower bowel —Routine examination of the lower bowel in asymptomatic patients over 45 years of age has disclosed polyps in 3 per cent (93), 8 per cent (94), and 7 to 12 per cent (95) In about 70 per cent of the cases the polyps are single, the remainder multiple, and the estimated incidence of malignancy in these polyps ranges from 0 1 to 10 per cent Bacon *et al.* (96) found that of 800 cases of carcinoma of the large bowel, 15 per cent appeared to develop in adenomatous polyps; all polyps should be removed and biopsied, and the patient carefully followed for further appearance of polyps Multiple polyposis has a high incidence of neoplastic change, and Bartlett & Peck (97) recommended ileostomy and resection of the large bowel for this disease Carcinoma has occurred in 12 of 316 cases of chronic ulcerative colitis, an incidence of 3 8 per cent, and five of these latter patients showed pseudopolyposis (98) The average age of onset of the ulcerative colitis and carcinoma was 28 3 and 44.3 years, respectively. Loeb & Scapier (99) have described a method for obtaining washings from the rectosigmoid area for cytological examination. Blank & Steinberg (100) have obtained positive diagnoses of rectal cancer from smears taken from the surface of the growth, but not from the discharge below the lesion. In 102 cases treated by abdominoperineal resection, Dunning *et al* (101) reported a five-year survival of 53 per cent and a 10-year survival of 41 per cent. Welch (102) reviewed the results of treatment in 1,966 cases of large bowel cancer seen at the Massachusetts General Hospital; the five-year survival in the total series

in nine patients, repeated every three to four months, to be a satisfactory method of administering estrogen therapy. Two of three patients, refractory to castration and further estrogen therapy, were improved by testosterone therapy, although their serum acid phosphatase activity increased (72), and Trunnell *et al.* (73) have obtained varying degrees of improvement with progesterone in 7 of 10 patients who had relapsed following castration or estrogen therapy. The treatment, however, was poorly tolerated. Huggins & Bergenstal (74) have reviewed the indications for adrenalectomy, and they have reported on two patients, refractory to further hormone therapy, who were benefited by bilateral adrenalectomy and cortisone maintenance therapy.

Bladder cancer.—The management of neoplasms of the urinary bladder remains an exceedingly difficult problem. Because of the inadequacy of biopsy diagnosis, Thomas *et al.* (75) advised careful exploration before undertaking radical surgery. Flocks (76) has reviewed his results in 540 cases; ureterosigmoid anastomosis is considered a useful palliative procedure in inoperable cases. The results of treatment in 700 cases were analyzed by Colby & Kerr (77); if the bladder muscle were invaded at operation, the five-year survival was poor (about 10 per cent) regardless of the form of treatment, if the muscle were not invaded, the five-year survival was 64 per cent, and the cases treated by cystectomy showed a decreased survival rate because of complications resulting from the operation

Renal cancer.—Examination of the urinary sediment has occasionally been useful in the diagnosis of bladder and renal cancer (78). De Veer & Hamm (79) have made an extensive presentation of their experiences with various types of renal neoplasms. Hypernephromas may frequently present solitary metastases in the brain, and Störtebecker (80) suggested that they be removed when possible.

Gastrointestinal Cancer

Stomach and esophagus.—On the basis of statistical studies, Stock (81) has postulated the presence of irritant factors in the environment which may contribute to gastric cancer. Lampert *et al* (82) found that 13 per cent of gastric ulcers, believed to be benign preoperatively, were malignant at operation and 43.5 per cent of the patients with cancer have survived five years or longer. Boudreau *et al.* (83), in a study of gastric lesions in 234 autopsied cases over 50 years of age, found that the location of the ulcer in the stomach was of no value in predicting the presence of cancer. Cytological techniques for diagnosing gastric cancer are not entirely satisfactory, but they are being improved. Seybolt *et al.* (84) obtained positive diagnoses in only 40 to 60 per cent of patients with known gastric cancer, and the results have been poorer in carcinoma of the esophagus and pancreas The use of an abrasive, inflatable balloon to increase the exfoliation of cells (85) and the instillation of a papain (a proteolytic enzyme) solution to digest gastric mucus (86) may increase the accuracy of the method.

the relationship between polycythemia vera and the subsequent development of leukemia, which occurred in about 2 per cent of the cases, and they suggested that the high incidence of leukemia may be caused by the irradiation therapy used in polycythemia vera. Lanman *et al.* (117), on the basis of their studies showing that the vascular bed of the lungs efficiently removes leucocytes from the circulation, have suggested that leukemia may be due to a defect in the mechanism for the removing of leucocytes. A technique of cross-circulation in humans developed by Bierman and his group (118) is being applied to this and other hematological problems

The remarkable but transient results from treatment in some cases of acute leukemia have increased interest in this disease. Southam *et al.* (119), Bierman *et al* (120), and Rodgers *et al* (121) have reviewed its natural history, and their reports provide a base line for measuring the value of various forms of therapy. The temporary beneficial effect of the 4-amino derivatives of folic acid have been well defined. The best results are obtained in children. Burchenal and his group (122) obtained good responses in 19 of 60 children and 1 of 28 adults, and significant prolongation of life occurred in the patients responding to therapy. Four of 29 patients also showed some improvement associated with the administration of 2,6-diaminopurine, a purine antagonist. Laski *et al.* (123) obtained complete or partial remissions in 14 of 53 children with the folic acid antagonists The folic acid antagonism may be overcome by folinic acid (citrovorum factor), which appears to be the activated form of folic acid, this factor will protect mice (124) and man (125) against large doses of the antagonist; unfortunately however, both the host and tumor cells appear to be equally protected. Corticotropin (ACTH) and cortisone induce a high incidence of remissions (50 to 60 per cent) in acute leukemia in children, but less frequently in adults (126, 127, 128). These remissions are usually of short duration, but two or three may be obtained in responsive children. ACTH and cortisone and the antifolics act independently in leukemia, and patients refractory to one agent may obtain a temporary remission from the other (129). The ultimate development of resistance to therapy in responsive patients is a distressing but provocative problem. Burchenal *et al.* (130) have developed a line of resistant leukemic cells in mice from a strain originally susceptible to the antifolics, and Law & Boyle (131) have obtained three such lines of transplantable resistant cells, one of which grows optimally in the presence of a folic acid antagonist (132)

Shimkin *et al.* (133) have analyzed the incidence, distribution, and survival time in chronic myelogenous leukemia during the years 1910 to 1948; they conclude that despite the introduction of new forms of therapy there has been no substantial change in the mean survival time, which persists between three to four years after apparent onset of the disease Their results of treatment with radioactive phosphorus have been reported by Diamond & Craver (134) and Osgood (135); the latter report emphasizes that the patients were able to live normally during more than 80 per cent of the

was 25 per cent, and the survival in the patients resected was 45 per cent. Their more recent cases (1944 to 1948) showed an estimated over-all five-year survival of 32 per cent.

Pancreas.—Miller *et al.* (103) reviewed the clinical and post-mortem findings of 202 cases; 71.3 per cent were in the head of the pancreas, 28.7 per cent in the body. The disease was twice as common in males, and the average age at onset was 60.7 years. In a study of 102 cases (104), 94 were explored, 41 were palliated with a biliary-intestinal anastomosis, and eight were resected. Two of these latter cases are alive, one with recurrences, 24 weeks postoperatively. The palliative procedures did not prolong life, the average survival time being 25 to 26 weeks. The autopsy findings in 100 cases of carcinoma of the pancreas were reported by Mikal & Campbell (105) from the Boston City Hospital; 18 of the patients were considered operable at autopsy. Thrombophlebitis was presented in 28 per cent of the series.

Liver and gall bladder.—The incidence of primary carcinoma of the liver is increased in patients with portal cirrhosis. McNamara (106) reported that 11.6 per cent of patients with cirrhosis have primary hepatic carcinoma, and 73 5 per cent of patients with hepatic carcinoma had cirrhosis of the liver There did not appear to be an increased frequency of other types of cancer in hepatic cirrhosis (107), and the incidence of carcinoma of the prostate is also unchanged (108). These reports suggested that hormonal alterations resulting from hepatic insufficiency did not appreciably change the incidence of cancer. Russell & Brown (109) found that the incidence of carcinoma of the gall bladder in the presence of gallstones is probably less than 0.66 per cent and concluded that cholecystectomy for cholelithiasis as a means of preventing cancer was not justified. In their 29 cases of carcinoma of the gall bladder, only seven patients were resectable, and none were cured. Berman (110) has written an excellent monograph on primary cancer of the liver.

Leukemia, Lymphomas, and Allied Disorders

Leukemia.—Excellent reviews of the recent literature have been prepared by Kirschbaum (111) and by Furth (112). Gross (113) has reported that centrifuged extracts of leukemic cells or of embryos from a high leukemia strain of mice (AK strain) when injected into a low leukemia strain (C_3H) within a few hours to several days after birth induced spontaneous leukemia in a high percentage of the mice when they reached 6 to 19 months of age. Some of the offspring of these C_3H mice also developed leukemia. Gross suggested that leukemia is produced by a cell-free particle apparently transmitted through the embryo in utero Anderson (114) observed the occurrence of acute leukemia in five of eight siblings. The incidence of leukemia over a 20-year period in radiologists was nine times greater than among general physicians, accounting for 4.68 per cent as compared to 0.51 per cent of deaths, respectively (115). Schwartz & Ehrlich (116) critically reviewed

1,871 surgically removed thyroids, but of 1,148 nodular goiters in this group, 4 5 per cent contained carcinoma. They commented on the high incidence of thyroid cancer found surgically, and its relative rarity as a cause of death. Perloff & Schneeberg (155) reviewed 49 cases of thyroid cancer, and in 38 per cent several pathologists were in disagreement as to the diagnosis of cancer Crile (156) and Hare & Salzman (157) presented their experiences and survival rates in various types of thyroid cancer, and Frazell & Duffy (158) reviewed 40 cases of Hurthle cell cancers of the thyroid. Twenty-eight cases of thyroid cancer in children were analyzed by Duffy & Fitzgerald (159); 15 were papillary carcinoma, eight alveolar or follicular, four solid tumor and one unclassified Twenty-six of the 28 patients had cervical lymph node metastases, and in 25 of the 28 cases the disease began around puberty. Nine of the group received low-voltage x-ray therapy for an enlarged thymus early in life; this also has been reported in another case (160). Rawson *et al.* (161, 162) have critically reviewed the effect of radioactive iodine in 146 cases of thyroid cancer; 20 were suitable for I^{131} therapy, and in 10 cases (6 8 per cent of the group) histological or x-ray evidence of tumor destruction appeared Their criteria for I^{131} therapy are: (*a*) inability to remove the tumor surgically, (*b*) demonstration that the tumor can concentrate I^{131} (this ability can be increased by destruction of the normal thyroid and by pre-treatment with thiouracil) and (*c*) the calculated total body dose of irradiation should not exceed 500 r e p

Central Nervous System

Several techniques are being developed to improve the diagnosis and localization of brain tumors, before and during surgery Selverstone & White (163) have used radioactive phosphorus or potassium, and the tumor has been mapped with a fine probe counter during surgery. Davis *et al* (164), using radioactive diodofluorescein, and scanning the skull with a graphic recording counter, obtained approximately 95 per cent accurate diagnosis and localization. Localization of tumors in the spinal cord is much more difficult because of radiation from the visceral organs In physical studies with the radioactive fluorescein technique, Moore (165) has discussed in detail the technical problems of tumor localization. In contrast to the American findings, de Winter (166) reported that radioactive fluorescein failed to diagnose 19 out of 20 verified brain tumors. Wrenn *et al.* (167) has used a positron emitter (Cu^{64}) incorporated in a dye, and French *et al* (168) are attempting to apply pulsed ultrasonics to localize brain tumors Mabon *et al* (169) have reviewed the pathological picture in 131 cases of astrocytomas of the cerebellum. Their average postoperative survival ranged from six to seven years. Peirce & Bouchard (170) have reported their results on the use of x-rays in the treatment of tumors of the brain and brain stem. They obtained some prolongation of life; glioblastoma multiforme survived an average of 15.6 months, 43.9 per cent of the astrocytomas have survived three years, and 24 3 per cent were alive at six years, and the survival of the

duration of the disease. Stroebel *et al.* (136) summarized their experiences with 199 patients with polycythemia vera treated with radioactive phosphorus, and this agent appears to be the most effective treatment available.

Lymphomas.—There is a suggestion of an increase in familial incidence of Hodgkin's disease according to Mazar & Straus (137). Bichel (138) reviewed the association of Hodgkin's disease and pregnancy, and concluded that it is not exacerbated by pregnancy. The nitrogen mustards have a well-defined and established role in the management of the lymphomas and allied conditions (139, 140). Gellhorn & Collins (141) found in Hodgkin's disease that nitrogen mustard caused improvement in 78 per cent of their cases of Hodgkin's disease; the need for x-ray therapy was diminished, but survival time was not significantly prolonged. In his monograph on Hodgkin's disease, Craver (142) reported that the per cent of five-year survivals in his series had increased from 17.7 per cent of those patients seen during 1918 to 1935 to 23.6 per cent of those seen during 1930 to 1943. Triethylene melamine (TEM), a compound closely related pharmacologically to nitrogen mustard, also has a range of therapeutic activity similar to that of nitrogen mustard (143, 144, 145). This agent, furthermore, is effective by mouth, and it has been useful in the treatment of ambulatory patients. ACTH and cortisone are of occasional benefit in the lymphomas (126, 127).

Multiple myeloma.—This disease is being diagnosed more frequently with the increasing awareness of its many clinical manifestations, which have been ably summarized by Limarzi (146). Three cases, presenting no evidence of bone lesions by x-ray examination, were diagnosed by bone marrow aspiration (147). Rundles and his group have continued to report on the beneficial effects of urethane therapy, describing relief of pain, interruption in progression of bone lesions, and, sometimes, recalcification (148) and reduction of abnormal serum proteins (149). Urethane therapy should be started as early as possible in the disease, since it has not been as effective in the far-advanced cases. Lawrence & Wasserman (150) obtained some improvement in 5 of 20 patients treated with radioactive phosphorus and radioactive strontium. ACTH and cortisone have produced relief of pain, and improvement in serum proteins in an occasional patient (126, 127).

Thyroid Cancer

Morris & Green (151) induced thyroid tumors in mice with thiouracil, and found that these tumors gradually achieved autonomy after several passages through thiouracil-treated mice. A variety of thyroid neoplasms was obtained in rats treated with radioactive iodine by Goldberg & Chaikoff (152). The frequency of the occurrence of cancer in solitary adenomas and nodular goiters remains the subject of discussion, although the consensus is that these tumors should be removed surgically. Lahey & Hare (153) reported that 10 per cent of solitary adenomas of the thyroid are malignant, whereas the incidence is about 0.6 per cent in multiple nodular or nodular toxic goiters. Zimmerman *et al.* (154) found 5.4 per cent benign adenomas in

Other tumors.—Primary reticulum cell sarcomas of bone are radiosensitive and run a relatively benign course, and Coley *et al.* (185) reported a five-year survival rate of 47.6 per cent. The five-year survival rate in 78 cases of fibrosarcoma of the extremities treated by Ivins *et al.* (186) was 38 per cent; amputation was rarely the primary form of treatment, and there was no evidence that x-ray therapy increased the cure rate. McCarthy & Pack (187) have reviewed the clinical course of 56 cases of malignant tumors of blood vessels, including 36 cases of Kaposi's sarcoma. One hundred and fifty cases of tumors of the heart have been reported by Prichard (188), and Glassy & Massey (189) have reviewed the clinical literature. Seybold *et al.* (190) reported 45 cases of thymic tumor, 34 of whom had symptoms of myasthenia gravis Since these tumors cannot be diagnosed accurately by radiographic or clinical methods, exploratory thoracotomy is indicated when possible. Twenty-two cases of carotid body tumors have been analyzed by Lahey & Warren (191); these tumors are benign, surgery hazardous, and they should not be removed unless severe local sympotoms are present. Reese (192), in a recent monograph, has completely covered the field of tumors of the eye.

Tumors in Children

One to 2 per cent of all cancer occurred in children, and cancer, including leukemia, was the cause of death in 7.3 per cent of children dying between the ages of one and 14 years in 1948 (193). Andersen (194) has reviewed the children's tumors seen in Babies Hospital in New York during 1935 to 1950; there were 768 benign and 175 malignant tumors. Most malignant tumors in children fall in six groups: tumors of the nervous system, retinoblastomas, lymphomas and leukemia, bone tumors, tumors of the kidney and adrenal glands, and soft tissue tumors of mesodermal origin. Merriam (195) has analyzed the autopsy findings of 17 children with retinoblastoma; these patients showed both local extension of the disease into the brain, and generalized blood-borne metastases The cure rate in neuroblastoma is about 10 per cent according to a review by Beck & Howard (196), who reported an apparently cured case, but Wittenborg (197), in a selected group of 73 cases, has reported 20 apparently cured patients, a cure rate of almost 30 per cent. In Wilm's tumors, Higgins (198) reported apparent cures in 4 of 34 patients in his series; Harvey (199) recommended surgical excision followed by postoperative irradiation, and has obtained apparent cures in 41 5 per cent of children treated under one year of age, and 18 4 per cent over one year of age. He noted that Wilm's tumor has sometimes been cured by x-ray therapy alone, but reliance on this procedure for cure is unjustified. Arnheim (200) reviewed 44 cases of retroperitoneal teratomas, the malignant ones have a very poor prognosis, but he has records of 10 survivors in the benign group. Forty patients with sacrococcygeal teratomas have been reported by Gross (201); 29 have been cured by surgery, and the most satisfactory results have been obtained with early excision The relationship of the reticuloendotheliloses-eosinophilic granuloma, Letterer-Siwe's, and Hand-

undiagnosed gliomas were intermediate. Woltman *et al.* (171) have reviewed the clinical course of tumors of the spinal cord and filum terminale; the average survival time ranged from 6 to 13 years, many surviving longer. Gliomas of the cord were not as malignant as those of the brain. Deaths were frequently caused by urological infections, but antibiotic therapy may diminish this complication.

Miscellaneous Tumors

Skin.—Sullivan (172) reported the use of repeated applications of podophyllin in skin cancer, with satisfactory results in 19 of 20 cases. The majority of the tumors subsequently recurred, and Kern & Fanger (173) further demonstrated the interesting but transient effects of podophyllin in skin cancer.

Head and neck.—James *et al.* (174) have discussed the use of nylon threads containing radioactive cobalt (Co^{60}) in 40 cases of cancer of the head and neck. These threads may be placed at intervals, and they have been particularly useful in treating large, irregular masses. H. Martin *et al.* (175) strongly questioned the value of prophylactic neck dissection in cancer of the oral cavity, but a radical neck dissection should be undertaken if evidence of recurrence appears in the cervical nodes. C. L. Martin (176) has obtained regression of metastatic cervical nodes with x-ray therapy and interstitial radium, and he reported 27.3 per cent of 146 patients with palpable metastatic cervical nodes alive five years postoperatively. Hendrick *et al.* (177) have analyzed their experiences with 141 cases of salivary gland neoplasms

Melanoma.—Decker & Chamness (178) reviewed 25 cases of melanocarcinoma of the foot, and their results have been discouraging in that only one patient appears to have been cured. Of 68 cases seen by Adelson (179), 24 are surviving, and 20 have lived more than four years. While recognizing the possibility of late metastases in some cases, he reported a 36 per cent survival rate at four years. Pack & Scharnagel (180) have observed 1,050 cases of malignant melanoma, of which 32 were associated with pregnancy. They thoroughly discuss the management of melanoma in pregnancy, and emphasize the value of extensive and persistent surgery. Of patients followed more than one year, and some for much longer periods, eight of 23 were alive without apparent disease

Synoviomas.—Wright (181) analyzed 85 cases of giant cell synoviomas these occurred most commonly on the digits, and 40 per cent followed injury. These lesions are benign, but in 44 per cent of 54 patients followed, recurrences followed surgical excision. Of 17 cases of malignant synovioma treated by Hale (182), four have survived longer than five years. Pack & Ariel's (183) 60 cases of malignant synoviomas represented 8.4 per cent of neoplasms occurring in the soft parts. They obtained a five-year survival of 23.5 per cent by widespread excision and amputation in suitable cases; and x-ray therapy was useful for palliation of inoperable cases. Tillotson *et al.* (184) obtained five-year survivals in only 4 of 31 cases, and only one of these patients appears to be free of disease.

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Schuller-Christian's diseases has been critically reviewed by *Siwe* (202) and *Freud* (203). *Childs & Kennedy* (204) have obtained good responses with radiotherapy in 9 of 12 children with reticuloendotheliosis.

CANCER DIAGNOSIS

The methods for obtaining exfoliating cells and diagnosing the presence of cancer are being improved constantly, as already noted for cervix (10, 11), prostate (64, 65), bladder (78), lung (52, 53, 54) and gastrointestinal cancer (84 to 86, 99). The staff of the Vincent Memorial Hospital in Boston has prepared a book on the cytologic diagnosis of cancer (205). *Gladstone* (206) has demonstrated the value of the sponge biopsy method for the diagnosis of rectal, oral, and skin cancer. *Foot* (207) concludes that correlation between cytologic smears and microscopic sections is good in cancer of the genital and respiratory tracts, fair in the urinary tract, and poor in the alimentary tract. Liver (208) and splenic (209) aspiration biopsies have proved useful in the diagnosis of lymphomas, leukemia, and metastatic cancer. Bone marrow aspiration produced evidence of metastases in 71 of 152 patients with cancer, and metastases were most commonly found in neuroblastoma and carcinoma of the prostate and breast (210). *Jonsson & Rundles* (210) suggested that some of the anemias occurring in cancer may be due to bone marrow replacement by tumor cells, but *Schen & Homburger* (211) do not believe this is an important mechanism.

A large number of serological tests has been proposed as useful in the diagnosis of cancer, including the thermal coagulation and iodoacetate tests, methylene blue test, level of mucoprotein test, Bolen test, and antiproteolytic reaction, but critical evaluation of these tests continues to show them to be nonspecific (212 to 215), and they appear to be of little practical value *Sobotka* (216) has critically reviewed the basis for some of these cancer tests and, while he finds no evidence that alteration in the blood has been found in cancer, he believes that "it is plausible to fish in the protein pool for cancer-specific features." *West et al.* (217) found that rapid tumor growth is associated with a high antichymotrypsin and low antirennin values, and these enzyme activities are reversed when the disease is inactive or the tumor is regressing. Radioactive gallium (Ga^{72}) has been shown by *Mulry & Dudley* (218) to localize to a greater degree in osteogenic and osteolytic lesions, and it has been used in diagnosing tumors in bone

CHEMO- AND EXPERIMENTAL THERAPY

The search for chemotherapeutic agents to treat cancer has become a major scientific enterprise. The laboratory and clinical studies are intimately connected, but only the latter will be considered here Triethylene melamine (TEM), a substance closely allied to nitrogen mustard, is now available for clinical use (143, 144, 145), and other analogues of TEM are under study (219). Urethane is used in multiple myeloma (148, 149), but its general

usefulness in this disease has not been established. Ohler *et al* (220) reported a case of hepatic necrosis apparently following urethane therapy Cortisone and ACTH are of transient value in the lymphomas, and may cause remarkable improvement in acute leukemia, particularly in children (122, 123). Another antimetabolite, 2,6-diaminopurine, seemed to have an irregular but occasionally beneficial effect in leukemia, but 8-azaguanine (guanazolo), an agent producing tumor regressions in mice (223), has, thus far, failed to show any therapeutic activity in man (224, 225) Lang (226) has reviewed the work on radioactive gallium, and presents evidence that in 12 patients radioactive gallium appeared in high concentration in metastatic lesions in bone. He suggested that this isotope may be useful in treating osseous metastases Paraoxypropriophenone, reported to be a potent pituitary inhibitor, and effective in a case of chorioepithelioma (227), has been found to have no inhibitory action against the rat pituitary (228). In a remarkable episode, Durovic and Ivy sponsored the use of a secret substance, named Krebiozen, for the treatment of cancer. This substance was alleged to be prepared from horse serum, but no acceptable assay method was presented to indicate the presence of an active substance Krebiozen, subsequently, was investigated in many clinics, and was found to be without demonstrable therapeutic activity (229).

Klopp *et al.* (230), by means of an intra-arterial catheter, developed a technique for injecting nitrogen mustard in fractionated doses into arterial supply to tumors They obtained temporary regressions and symptomatic improvement in tumors located in the head and neck and pelvis. Patients tolerated larger doses of nitrogen mustard by the intra-arterial as compared to the intravenous route, presumably because of the local fixation of the agent, and Bateman *et al.* (231) showed that the bone marrow exposed to the intra-arterial injection was more severely depressed than the bone marrow not directly treated Independently, Bierman *et al.* (232, 233) treated neoplastic disease in the extremities and in the liver with nitrogen mustard. This work entailed the development of techniques for identifying and catheterizing major visceral arteries with catheters introduced under local anesthetic into the brachial artery (234) Muller & Rossier (235) have studied the effects of radioactive gold and zinc in neoplastic disease of the lung by injecting them into a cardiac catheter introduced into the pulmonary artery.

Under the impetus of Moore (236) studies are in progress to develop strains of oncolytic viruses which will selectively localize in mouse and human tumors Southam & Moore (237), in a preliminary study, have inoculated patients with viruses (West Nile, Ilheus, and Bunyamwera) which are oncolytic in mice They obtained infections in 15 of 44 patients treated, but no significant effects on the growth of the neoplasm were noted Pack (238) treated 12 patients with melanoma with Harris rabies vaccine, and in two cases some evidence of tumor regression occurred. The virus of

feline agranulocytosis and lymphopathic venereum have been given by Bierman *et al.* (239) intravenously to patients with metastatic cancer and leukemia without substantial clinical improvement. Three children with acute lymphogenous leukemia showed temporary clinical and hematological improvement with varicella infections.

General Summary

No major developments or important new trends in cancer have appeared in the clinical literature during the past year. The search for carcinogenic factors in the environment is more intensive, and presumptive evidence has been adduced that environmental factors may be contributing to a substantial number of cases of carcinoma of the lung, cervix, penis, stomach, and to leukemia. Long-term and detailed record keeping and statistical study are necessary before definite conclusions can be drawn. Attention is also being directed toward the elimination of precancerous or potentially cancerous lesions. Surgery has been advised for many situations, including gastric ulcers, intestinal polyps, carcinoma of the cervix *in situ*, thyroid adenomas, cholelithiasis, and removal of the uninvolved breast when the other breast contains cancer (240). When the pathologist develops a more satisfactory basis for predicting the biological behavior of a tumor, and when the incidence of malignant change in various benign lesions is known, and the level of surgical competence has been generally raised, the indications for prophylactic removal of potentially cancerous lesions can be established clearly. In the individual case, the earlier the diagnosis of cancer the better the clinical result The numerous proposals of serological tests for cancer have been refuted on further study, and none of convincing usefulness exists. Cytological techniques for the diagnosis of cancer have been applied widely, and they are of unquestionable value in obtaining a presumptive diagnosis of carcinoma of the lung and cervix. Their use in other areas is largely reserved for interested experts working on selected problems, but this situation may be improved. With the increased medical interest in cancer, numerous signs and symptoms suggestive of certain types of cancer are being recorded.

The curative treatment of cancer is largely in the hands of the surgeons, although the radiotherapists have considerable control over carcinoma of the cervix, certain tumors of the head and neck, skin, and the lymphomas and leukemia. The statistical analyses of survival and cure rates are being standardized, but the problem of comparing end results in different series is a difficult one There has been no remarkable change in the cure rates of any type of cancer reported during the past year, and with the training of competent cancer surgeons and radiotherapists, the nationwide cure rates may approach the levels reached by the major institutions treating cancer today. Radical surgery has been extended to a variety of tumors in the hope of increasing cure rates and salvaging otherwise hopeless patients; the results are being evaluated, and judgment as to the benefits derived from these operations must be deferred.

Radiotherapy is being used prominently in the palliation of cancer. The objectives of treatment are limited; to relieve symptoms and control temporarily the growth of the tumor. The plan for a course of palliative therapy may be considerably different from that for treatment designed to be curative. The potentialities of chemotherapy, unlike those of surgery and radiotherapy, are unlimited in the treatment of cancer, and steady progress is being made During the year triethylene melamine, a nitrogen mustard-like compound suitable for oral use, ACTH and cortisone, and the folic acid antagonists have established their place in the palliative treatment of certain types of cancer, particularly leukemia and the lymphomas.

In continuing cancer research lies the ultimate hope of providing the clinician with solutions to his many diagnostic and therapeutic dilemmas. The diverse and intensive studies on cancer have resulted in many fundamental findings in biology, chemistry, and physics, and some of these observations have found effective clinical applications While there does not appear to have been any important new knowledge concerning cancer developed during the past year, only in retrospect will we know whether an observation on cancer, equivalent to Fleming's original description of penicillin, was recorded in the literature during 1951.

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DISEASES OF THE NERVOUS SYSTEM[1]

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During the year 1950 to 1951 the literature on diseases of the nervous system and related studies in neurophysiology, neuroanatomy, neurochemistry, and neuropathology has been so extensive that we have not attempted to review it completely within the limits of this chapter. Only representative selected studies which seem of greatest interest will be mentioned; those which mark trends of thinking and progress in understanding of mechanisms of nervous action in health and disease. In so far as possible we have tried to bring neurophysiological and clinical studies together, even though the former may seem to have little immediate bearing on current problems in clinical neurology.

Dimercaprol and Hepatolenticular Degeneration

In the previous review Nielsen stressed the important new developments in our understanding of enzyme systems and their poisons in the neuritides and the beneficial effects of dimercaprol (BAL; 2,3,-dimercaptopropanol). It has now been found by Denny-Brown & Porter (1) and by Cumings (2) that patients with hepatolenticular degeneration (Wilson's Disease) may show dramatic recovery when treated with dimercaprol. Denny-Brown & Porter report five cases who have undergone prolonged treatment over a period of months by intermittent courses. A dosage of 2.5 mg. per kg resulted in recovery of bedridden patients, some of whom were violently ataxic, dysarthric, and with violent tremors All patients became able to take care of themselves with one exception, a patient in whom deterioration had reached a severe degree before institution of treatment. There was a marked increase in urinary output of copper during treatment Since excessive copper had been found in the brain of patients with this disease, it seems clear that this disease is due to an abnormal accumulation of copper compounds in the brain and the resultant toxic action upon essential enzyme systems in nerve metabolism.

> This finding in a "degenerative" disorder that is commonly familial gives substance to the hypothesis that all such nervous diseases result from the cumulative effects of by-products of "inborn errors of metabolism" and offers hope for the ultimate solution of their problems (1).

It is likely that further similar advances in our knowledge of metabolic factors in disease of nerve and brain will gradually lessen the number of conditions for which the neurologist can now provide only a diagnosis.

[1] This review covers approximately the period from June, 1950 to December, 1951.

Multiple Sclerosis and Demyelinating Diseases

A number of interesting reports have appeared on the clinical evaluation and possible etiology of multiple sclerosis. Alexander (3) presents for long-term evaluation of therapy a scoring method based on 50 variables derived from neurologic examination and on "critical levels" of the score related to degree of interference with the patient's ability to get about. Decrease in motor power and visual acuity was noted by Guthrie (4) in patients with multiple sclerosis as a response to partial or total body heating. Pratt *et al.* (5) found in a total of 310 cases a familial incidence of 6.5 per cent which was higher than that expected by chance, and they conclude that heredity plays some part in the predisposition to this disease.

Campbell *et al.* (6) review the case for lead in relation to multiple sclerosis and conclude that it does play some part, possibly by interfering with some mineral, vitamin, or enzyme reaction and thus precipitating demyelination. In a trial in 42 patients, tetraethyl-ammonium chloride was found to cause no improvement in over-all or detailed neurological signs (7) Symptomatic improvement may occur in some cases with corticotropin (ACTH) or cortisone (8). A type of colloidal gold reaction described by von Storch *et al* (9) was found in 158 cases of multiple sclerosis and in only 36 per cent of cases with miscellaneous nervous diseases.

Mutlu (10) has confirmed previous studies that capillaries of the nail beds of patients with multiple sclerosis show abnormalities consisting of thin, small, spastic, fragmented appearance with slow or interrupted circulation. The same changes were seen in patients with other neuropsychiatric disorders Fifty patients with multiple sclerosis showed lower capillary resistance than 50 controls, but the test was not found useful for evaluation of the severity or prognosis in individual patients (11).

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daily intake of animal fat is also highest. The effect of fat on the blood composition was studied because of the possibility that clumps of fat particles (chylomicra) or of red corpuscles may be a source of capillary emboli responsible for demyelinating lesions High fat diet, pregnancy, and relatively large doses of heparin increase the tendency of chylomicra to cluster and associated with this is an increased tendency for the red blood corpuscles to undergo packing and distortion (13) In dogs these changes were accompanied by alterations in the plasma protein pattern of the paper chromatogram, and similar protein changes were found in patients with multiple sclerosis during exacerbations with reversion to normal during remissions (14, 15)

Chemical studies in 50 patients with multiple sclerosis and 30 controls were carried out after the ingestion of glucose (16) An increase in pyruvic acid in the blood was found out of proportion to the level of lactic acid. Serum cholesterol was also high and was elevated more in patients with active disease.

A developmental disorder of lipid metabolism has been considered by Brain & Greenfield (17) as the basis for late infantile metachromatic leucoencephalopathy which occurs in the second or third year of life and is characterized histologically by (*a*) disappearance of the interfascicular oligodendroglia from the white matter of the cerebrum and from many areas in the brain stem, cerebellum, and spinal cord and (*b*) demyelinization affecting mainly those fiber systems which myelinate after birth. The early symptoms are disorders of motility and equilibrium, with dementia later.

In an experimental study, Lumsden (18) produced a constant symmetrical lesion of the central white matter in the rat by chronic potassium cyanide intoxication. The lesion is unlike multiple softenings produced by microembolization by carotid injection of coagulants. It is considered that the cyanide has an affinity for enzymes necessary for the preservation of the myelin sheath. Once the lesion is established it progresses, consistent with the idea that a myelinolytic agent is then derived from the focus in the white matter.

Treatment of Meningitis

By means of persistent daily administration of streptomycin in doses of 100 mg. intrathecally for 6 to 12 weeks or longer combined with doses of 2 gm. intramuscularly for not less than 6 months, the group in Oxford (19, 20) have been able to achieve a recovery rate of 50 to 60 per cent in over 60 cases of tuberculous meningitis followed for more than one year. It seems possible that the recovery rate can now be even further improved by the supplemental injection intrathecally of minute amounts of purified protein derivative of tuberculin (PPD) which is responsible for dissolution of the exudate in the subarachnoid spaces in tuberculin-sensitized patients. Two hopeless cases unexpectedly recovered completely, and a third case improved dramatically for a time following this treatment.

Asenjo *et al* (21) report in 159 cases increasingly successful results with the surgical removal of focal tuberculous lesions of the brain when combined with streptomycin treatment.

On the basis of Teng's (22) experience, intrathecal administration of bacitracin appears to be of value for septic meningitis which fails to respond to penicillin and sulfonamides

Angiography and Cerebral Circulation

Over the past ten years the widespread adoption of carotid angiography as a diagnostic method for intracranial lesions, particularly those of a vascular nature, has been favored by application of the technique of percutaneous puncture of the vessel and the availability of relatively innocuous organic iodine contrast media, such as iodopyracet (Diodrast), in place of radioactive colloidal thorium dioxide (Thorotrast) In many clinics, especially in Norway and Sweden, where the percutaneous method has been most extensively developed, angiography is now carried out in preference to air studies, often

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Swank (12) has found that the incidence of multiple sclerosis may be related to dietary fat, and detailed nutritional surveys instigated by him in Norway show that the highest incidence is found in farming areas where the daily intake of animal fat is also highest. The effect of fat on the blood composition was studied because of the possibility that clumps of fat particles (chylomicra) or of red corpuscles may be a source of capillary emboli responsible for demyelinating lesions. High fat diet, pregnancy, and relatively large doses of heparin increase the tendency of chylomicra to cluster and associated with this is an increased tendency for the red blood corpuscles to undergo packing and distortion (13). In dogs these changes were accompanied by alterations in the plasma protein pattern of the paper chromatogram, and similar protein changes were found in patients with multiple sclerosis during exacerbations with reversion to normal during remissions (14, 15)

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angiograms with only three deaths, all of which occurred in cases of large expanding intracranial lesions, and were not necessarily related to angiography. Differences in incidence of complications following angiography may be due in part to the selection of cases or to variations in toxicity among different batches of the same injection medium as shown experimentally by Smith *et al.* (30). However, iodopyracet has been shown experimentally to cause seizures and to produce severe abnormalities in the EEG and increased permeability of the cerebral blood vessels when injected into rabbits and monkeys (31, 32). Injections repeated at short intervals may have more injurious effect on the cerebral vessels than the same amount of the dye given at a single injection (33).

In a brief monograph on the cerebral circulation in health and disease, Schmidt (34) gives a critical assessment of the present state of knowledge of cerebrovascular physiology, and presents many interesting results derived from using the nitrous oxide method of Kety for determination of cerebral blood flow in patients with various vascular disorders, and evaluates the effect of drugs on cerebral circulation. This excellent review should be consulted in the original A revision of the finding that stellate block has an insignificant effect on cerebral blood flow, as reported earlier, may be required since it is now reported (35) that after stellate ganglion removal in seven patients there was a significant decrease in cerebrovascular resistance, the greatest effect being apparent in patients with the initially slowest blood flow.

A valuable experimental approach to the problem of cerebrovascular disease was carried out by Harvey & Rasmussen (36, 37) who occluded the middle cerebral artery in monkeys for varying periods or permanently. The degree of hemiparesis was related to the duration of the occlusion, but permanent paresis was not obtained with occlusion of less than 15 min. Manipulation of the middle cerebral artery caused constriction at the site of manipulation and of all the vessels in the exposed hemisphere Clinical epileptic seizures appeared in three animals following occlusions of not more than 40 min and EEG abnormalities appeared in two-thirds of the 19 monkeys studied

Anderson (38) was able to show by vascular injection of iodopyracet that the vertebral venous system may be considered a continuous chain of vessels extending from the pelvis to the cranial venous sinuses. The venous pressure in this system is relatively low and subject to variation depending upon posture, gravity, and respiratory excursions, and his studies add additional support to previous observations suggesting that tumors or infections may spread from the pelvic or thoracic regions to give intraspinal or intracranial complications

Fisher (39) has pointed out that thrombosis of the internal carotid rather than middle cerebral occlusion may often be a cause of hemiplegia. The features of continuous headache over the eye and absence of internal carotid pulsation should suggest the diagnosis. The carotid sinus is the site of pre-

by the radiologist or neurologist, and may be done concomitantly with pneumography. Not infrequently the procedure is performed on outpatients Indeed, the ease with which angiography may now be done is in striking contrast to the difficulties still to be met in attempting to treat the grave vascular lesions so disclosed.

From the recent literature, three main points emerge: (a) increasing success of surgical treatment in some clinics, (b) further evidence that the present injection media are toxic, and (c) a new method for vertebral angiography.

The importance of specific studies of each case in relation to possible surgical treatment is emphasized by Poppen (23). On the basis of his experience with 143 patients with intracranial aneurysms who underwent surgical treatment, he considers ligation of the carotid artery the procedure of choice for treating aneurysms confined to the bifurcations of the larger arteries of the circle of Willis Direct surgical exposure with clipping or excision of the aneurysm was successful in 25 out of 32 patients.

Detailed follow-up studies of patients whose vascular lesions were treated surgically are of value so that more adequate comparison with nonsurgically treated cases might be made. Even when the condition of the patient might be considered satisfactory (from clinical assessment), evaluation of serial electroencephalograms (EEG) may show residual cerebral damage as long as three years following operation (24).

Preoperative EEG studies sometimes show abnormalities in the area of brain supplied by the artery on which the aneurysm is situated (24). This may be due in part to vascular spasm of a main cerebral vessel which has recently been shown to occur in six cases with arterial aneurysms (25). Roseman *et al.* (26) report serial EEG studies in 42 cases of proven aneurysm. In the majority of cases, especially those with records taken during the first week following rupture, decrease in voltage, slow waves, or slowing of alpha rhythm, served to lateralize the aneurysm. A delta focus persisting longer than three weeks usually suggested an intracerebral hematoma.

Further evidence has accumulated from clinical and experimental studies that angiography with iodopyracet (Diodrast) is not without danger. Dunsmore *et al* (27), using 35 per cent iodopyracet, had 14 complications in 108 patients; there were three deaths, two of which were related to delayed massive cerebral infarction, four instances of permanent hemiparesis, two cases of transitory hemiplegia, two cases of convulsions, one case of carotid artery thrombosis, one case of injury to the cervical sympathetic chain, and one case of iodopyracet skin sensitivity. They conclude that patients over 50 years of age or those having thrombotic tendencies or impaired cerebral circulation are more liable to complications. It is of interest to note the results in 2,490 examinations by pneumoencephalogram over a six-year period in which Whittier (28) notes 24 deaths, six of which were significantly related to the procedure and all six being examples of large intracranial lesions. These reports are to be compared with Bull's (29) series of more than 2,000 carotid

brain, the limits of a tumor are defined at operation. For preoperative localization the more penetrating γ-rays are needed and radioactive potassium is stated to give a better concentration than diiodofluorescein (49) but has the disadvantage of being taken up by the temporal muscle and so obscuring its intracerebral locus

In attempts to utilize the energy of nuclear disintegration for radiation therapy of tumors, radioactive phosphorus proved of no value because it was also concentrated in other body tissues (47) and did not affect growth of the tumors (50).

An intriguing approach to therapy of tumors (Sweet and Javid) is suggested by the observation that slow neturons are "captured" by nuclei of some atoms with release of energy (47). When boron[10] captures a slow neutron, a high energy α-particle that results travels less than 15 μ in tissue, so that its destructive effect may be confined to a precise area. It has already been shown that borax can be concentrated from three to 38 times as much in some brain tumors as in brain, without significant toxic effects, so that the effects of irradiation with slow neutrons may be effectively directed toward the tumor

Diseases of Muscle and Neuromuscular Systems

Rabinovitch, Gibson & McEachern (51) have shown that patients with menopausal muscular dystrophy and dermatomyositis show marked improvement with wheat germ oil therapy, while other neuromuscular disorders failed to respond Shy & McEachern (52) then showed that the same disorders were improved by cortisone administration. ACTH or cortisone seriously aggravates myasthenia gravis [Shy *et al.* (53); Torda & Wolff (54)] and may result in death (one case), though some improvement may occur after repeated courses of treatment.

Buchtal & Madsen (55), with an ingenious electromyographic technique, reaffirm the observation that there is an abnormally high degree of synchronization in the discharge of motor units in anterior horn cell diseases, while Kugelburg & Taverner (56) show that the same holds true when motor units are activated by direct current electrical stimulation of their nerve supply, suggesting that peripheral as well as spinal mechanisms may be involved.

Spinal Reflexes

Neurophysiological studies of spinal reflexes have brought to light much new and precise information though still not immediately applicable to clinical problems in which the functional state of these reflexes forms the foundation of neurological examination. Attempts to apply these methods to man are being made by Magladery and [illegible] (57)

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direction for the thrombosis, and the basic pathological process is atherosclerosis of the vessel. Angiography can confirm the diagnosis (40) but Elvidge & Werner (41) note that failure of the artery to fill with contrast medium may not necessarily indicate a thrombus. In some of their cases, the EEG showed abnormal slow waves. They also caution that carotid thrombosis may be an unexpected arteriographic finding not associated with hemiplegia. Thromboangiitis obliterans is added by them and by Johnson & Walker (42) as an important cause, and the latter authors tabulate the significant points of 101 cases from the literature: no satisfactory treatment is reported and resection of the vessel to obviate reflex spasm eliminates the possibility of recanalization of the thrombus which has been reported in some cases.

A new approach to vertebral angiography has been made by Radner (43) who inserts a fine catheter into the radial artery, exposed in the mid-forearm, and follows its tip into the vertebral artery under fluoroscopy. In 200 successful injections, 198 showed filling of the basilar artery and posterior cerebral arteries, and in 69 injections both vertebral arteries were filled. The method is of diagnostic value in occipito-temporal tumors, and in some tumors of the posterior fossa. Pinealomas give a characteristic picture, and the method has been since reported to give information on the reduction of these tumors during the course of radiation.

Anastomosis of the internal carotid artery and internal jugular vein has been used in an attempt to increase the blood supply of the brain in mentally defective children, but Tarlov *et al.* (44) have shown that there is no increase of cerebral vessels as seen by the angiogram, and the main effect of the operation was diversion of blood into the opposite lateral sinus. In one case they noted progressive proptosis and in another subarachnoid hemorrhage, both patients being improved after repair of the arteriovenous fistula. Gurdjian *et al.* (45) showed, after carotid-jugular anastomosis in the monkey, no increase in the blood flow or oxygen tension in the sagittal sinus. These results seem to provide no physiological basis for this operation.

Radioactive Substances

Several clinics have been applying radioactive tracer materials for localization of intracranial lesions. Ashkenazy, Davis & Martin (46) report results in 340 patients using radioactive diiodofluorescein injected intravenously, after which concentrations are measured at various head positions. Deposition of the dye is greater in the more cellular and more vascular tumors. There were 17 inaccuracies in 340 cases of space-occupying lesions, making an over-all accuracy of 95 per cent.

Sweet (47) reviews the experience of the group at Boston [Selverstone & White (48)] with radioactive phosphorus which is concentrated from five to 100 times more in tumor tissue than in normal brain. Since its radiation particles travel only a short distance, it cannot be used for preoperative localization, but by means of a probe counter which can be inserted into the

visual and other sensations. It has projections to many parts of the brain stem, mid-brain, diencephalon, and to motor as well as to sensory and association areas of the cerebral cortex. Areas in the cerebellum facilitate or inhibit spinal reflexes or cortically induced movements. Mechanisms are present which make it possible for the cerebellum to be a "great modulator of neurological function," including sensory, association, and motor functions.

Extrapyramidal Diseases

Continued experimental neurosurgical procedures carried out on patients with diseases of the extrapyramidal motor system, and experimental studies in animals, have yielded important new techniques and data, some with definite therapeutic promise, though the pathophysiological mechanisms of these disorders still remain obscure.

An excellent review of neurosurgical procedures by Bucy (71) has appeared. Most of the evidence suggests that either intention tremor or the tremor at rest of Parkinsonism can be abolished only by complete interruption of the corticospinal tract, either by excision of motor cortex (area 4) or by section of the pyramidal tract, with resulting paralysis of voluntary movement. Choreoathetotic movements can be completely and permanently abolished by cortical excisions of the motor and premotor cortex, but not by section of the anterior columns of the cord. However, partial section of the cerebral peduncle as described by Walker (72) and by Wertheimer & Mansuy (73) may abolish tremor and torsion spasm with little increase in hemiplegia, suggesting that activity in extrapyramidal pathways may also play a role in these involuntary movements. This is confirmed by the cases described by Fenelon (74) in which Parkinsonian tremor was almost completely abolished by section of the ansa lenticularis without producing any signs of involvement of the pyramidal tract.

In a study of hemiballismus, Meyers *et al.* (75) concluded that this disorder can be caused by lesions within the contralateral neo-striatum, paleostriatum, thalamus, or postcentral gyrus as well as in the corpus subthalamicum or in its afferent or efferent connections. They describe an operation consisting of a linear section through the motor cortex, just anterior to area 4, which will reduce or abolish the ballistic movement with little permanent effect upon voluntary movement, though they admit that cortical ablation gives more complete and permanent results. Cobb *et al* (76) report the results of a similar operation in nine cases of Parkinsonism with no beneficial effects on either tremor or rigidity.

The use of a human stereotaxic instrument for the accurate destruction by coagulation of deep-seated structures in the brain is a most promising development in the neurosurgical approach to extrapyramidal diseases as well as to other conditions (77, 78) Talairach, Paillas & David (79) report permanent and marked improvement for one year in hemiballismus and Parkinson tremor by local coagulation of pallido-fugal fibers, and Spiegel & Wycis (80) report marked reduction or abolition of choreoathetotic move-

the efferent supply to the intrafusal fibers of muscle spindles (confirming the original demonstration by Leksell and the suggestion of O'Leary) regulating the sensitivity of stretch receptors within the muscle. They do not, in themselves, cause any visible contraction of the muscle itself. This efferent regulation of the sensitivity of stretch receptors provides a newly discovered mechanism which may be involved in disorders of muscle tone and coordination based upon proprioceptive sensation.

The afferent impulses from muscle spindles are conducted in large rapid (Group IA) fibers to the cord where they synapse with the cells of Clarke's column [Lloyd & McIntyre (62)], after supplying collaterals to motor neurones, and proceed exclusively to the cerebellum [Mountcastle *et al.* (63)] with no evidence for direct projection to the cerebral cortex. Impulses from stretch receptors in muscle tendons inhibit the knee jerk [McCouch *et al* (64)] and provide inhibitory impulses for an autogenetic self-regulation of muscle contraction [Granit (65, 66)].

Eccles & Rall (67) have found that the long lasting potentiation of monosynaptic spinal reflexes by tetanic stimulation of muscle nerves does not parallel the synaptic potential. They propose that synaptic knobs probably swell with repeated activation providing a mechanism for the more enduring plastic states in the nervous system (such as "memory").

Eccles (68) has recently come to the conclusion that synaptic transmission cannot be accounted for on the basis of any electrical theory of conduction, and that a chemical mediator must be invoked to explain observations made with ultramicroelectrodes which presumably record from within single anterior horn cells. It thus seems probable that chemical transmitters, which seem well established for autonomic ganglia and neuromuscular junctions, may also be required to explain conduction in central synapses, though the transmitting substance is probably not acetylcholine.

These neurophysiological studies which have been a closed book to most neurologists because of the highly specialized techniques and terminology employed, should eventually lead to a rational understanding of the disorders in deep reflexes and muscle tone which are used constantly as signs of various nervous diseases. The relationship between these spinal reflex mechanisms and their alteration by descending influences from supraspinal motor systems of the brain may be of even greater significance in application to clinical problems.

The Cerebellum

Neurologists who have been baffled and overwhelmed by the wealth of new knowledge gained from anatomical and physiological studies of the cerebellum during recent years would do well to read the review of Snider (69) and the monograph by Moruzzi (70) which necessitate a considerable revision of the traditional concepts of cerebellar function. These new facts establish the cerebellum as a highly differentuated structure, with topographically organized representation of somatic sensation, as well as auditory and

Ascending Reticular Projection Systems

Neurologists and neurosurgeons have long been aware of the critical importance of certain structures in the region of the third ventricle and aqueduct of Sylvius in relation to states of consciousness (sleep, coma, stupor, akinetic mutism, or catalepsy on the one hand, and arousal, emotional excitement, or sham rage on the other). It was also known that the electrical activity of the cortex was particularly sensitive to these same changes in the state of consciousness, general reactivity, or excitatory state of the brain. The anatomical structures in diencephalon and mid-brain which mediate this "arousal" response, with its characteristic effect upon cortical electrical activity, have been outlined in considerable detail in the experimental studies of Magoun and associates (88 to 92) who have described it as an "ascending reticular activating system" The hypothalamic portion of this system, which possesses certain special characteristics, has been studied in detail by Ingraham *et al.* (93). The particular features of the thalamic portions of this system in relation to lower levels had been previously outlined by Jasper and co-workers (94, 95) and called the "thalamic reticular system." The sudden loss of consciousness in petit mal epilepsy was thought to involve also some portion of this reticular network of the higher brain stem, with its diffuse bilateral projections to the cortex (96)[2]

The ascending reticular system is a closely interrelated multisynaptic network of neurones extending through the mid-brain, posterior hypothalamus, subthalamus, and thalamus with separate projections to the cortex independent of the specific afferent systems with their thalamic nuclear relays Lesions within this system produce akinesis even though principal afferent systems to cortex remain intact. Arousal can still be affected by direct electrical stimulation of this system or by afferent stimulation following complete destruction of specific afferent thalamic relay nuclei for sound, visual, and tactile sensation This is made possible by collaterals from sensory pathways which enter the reticular system below the thalamus.

The response of cortical sensory receiving areas to incoming sensory impulses can be modified by conditioning effects arriving over independent projections from the thalamic reticular system (97) Corticofugal projections, particularly from the frontal, parietal, and anterior limbic areas, into this central reticular network have been demonstrated (98). The importance of the anterior cingulate gyrus in relation to brain stem systems responsible for such clinical states as akinetic mutism in man has recently been emphasized by Nielsen (99)

The anatomical details and functional characteristics of the different levels of the ascending reticular system are still in dispute, but there can be no doubt that this system will play an important role in our understanding

[2] The details of these studies are beyond the scope of this review. We can mention *only a few salient features*

ments following lesions of the pallidum. No permanent pyramidal signs of impairment in voluntary movement resulted. It would seem, therefore, that even though the corticospinal tract *seems somehow involved in the mechanisms* of these involuntary movements, disordered discharges from striatal structures may be the more critical cause. This gives hope that some of these patients may be helped without the disabling effect of excision of the motor cortex or section of the pyramidal tract.

An excellent assessment of the medical therapy of Parkinson's disease has been reported by Schwab & Prichard (81) showing that only about a 25 per cent improvement can be expected from any drugs now available. Trihexyphenidyl (Artane) and Caramiphen-hydrochloride (Parpanit) were thought to be the most useful drugs, chiefly because of ease of administration and freedom from side effects.

The existence of distinct "suppressor areas" in the cerebral cortex (commonly used in hypotheses of mechanisms of spasticity and dyskinesia in extrapyramidal as well as other diseases of the motor system) is open to serious question in the light of the experiments of Sloan & Jasper (82, 83), Dunsmore & Lennox (84), Ward (85) and others. Facilitation as well as inhibition of movement and tonic movements can be elicited from presumed "suppressor" areas including the anterior cingulate gyrus. Most of the effects previously described as a slow depression in electrical activity of the cortex have been shown to be due to the phenomenon of spreading depression which probably has little importance in the normal function of the cortex. Immediate effects of stimulation of the anterior cingulate gyrus may be either an augmentation or decrease in the electrical activity of the cortex, or in many cases only local effects may be observed, such as after-discharge.

The importance of the limbic or rhinencephalic system in the inhibition (*with some facilitation as well*) of *spinal reflexes* and cortically induced movements, as well as upon respiration and gastric motility, has been beautifully shown in the comprehensive studies of Kaada (86), though no clear relationship was found between effects on motor functions and associated changes occurring irregularly in the electrical activity of the motor cortex.

Denny-Brown (87) in a penetrating analysis of extrapyramidal cortical motor function gives a very logical interpretation of "suppressor" or inhibitory functions suggesting that the premotor area (area FB or 6) contains "the suppressor portion of an excitatory-inhibitory network . . the suppressor side of the co-ordinating system is as essential as the motor component." We would agree that inhibitory (the term "suppressor" adds only to the confusion) and excitatory functions must exist together for coordinated movement, but the evidence that any given local area of cortex has *only excitatory or inhibitory functions is far from convincing* What is apparently an excitatory or inhibitory effect from cortical stimulation may be varied according to the balance of these two processes in subcortical motor systems which set the stage for cortically induced movements

Anatomical and experimental studies of Glees & Cole (107) have confirmed in the monkey the familiar recovery of function which occurs following local lesions of the precentral gyrus. They demonstrated that small lesions in the hand area caused scattered degeneration in the internal capsule and descending fiber degeneration not only to cervical levels of the cord but down to the lumbar region (as previously found by Sherrington). After recovery of function adjacent cortical areas produced the same movements as that obtained from the previously excised region.

These results, together with many others, are used by Walshe (108) in a renewal of his hypercritical attack on the "mosaic" conception of fixed and detailed localization of specific muscles in restricted foci in the precentral cortex. He chooses to ignore the detailed localization of specific movements found by Liddell & Phillips (109, 110) in animals, when an efficient stimulating current was employed. He describes as "physiologically meaningless" the extensive and precise observations of Penfield on localization in the precentral gyrus of the unanesthetized human cortex, in spite of repeated emphasis by Penfield that such results do not reveal the origin of voluntary movements which must rise from a higher level of neuronal integration. Any satisfactory theory of normal cortical function must include such solidly established facts as functional localization in the precentral cortex, even though overlapping does occur. It must be explained how one can voluntarily move the tip of the index finger alone, as well as how more complex movements are integrated. It is obvious that no rigid mechanistic view of such localization is warranted from experimental as well as clinical data, but the attack on the "mosaic" conception of the origin of voluntary movement is directed largely against a straw man.

Hemispherectomy in Infantile Hemiplegia

Surgical removal of an entire hemisphere of the brain in 20 cases of infantile hemiplegia has been shown by Krynauw to produce striking improvement (102). Most of the cases had epileptic seizures, mental deterioration, and severe behavior disorders. The entire hemisphere was removed including the putamen and sometimes the globus pallidus but not the caudate. All patients became free of attacks without medication. Motor performance was improved because of the reduction in spasticity. Sensory defects disappeared for the most part in several months. No speech defects were noted even with removals of the left hemisphere. EEG records which were grossly abnormal from both hemispheres before operation improved greatly suggesting that the contralateral disturbance was transmitted from the affected hemisphere.

Obrador & Larramendi (111) confirm the benefit of hemispherectomy in one case. They note particularly the improvement in EEG and clinical course. Cairns & Davidson (103) report similar dramatic results in three further patients followed for a year, with cessation of seizures and improvement in mentality and personality as assessed by intelligence and performance tests.

of the neurological mechanisms underlying states of consciousness, attention, and perhaps even in relation to the central integration of conscious mental processes.

THE MOTOR CORTEX AND PYRAMIDAL SYSTEM

Experimental and clinicopathological studies of the motor cortex and pyramidal tract in relation to voluntary movement and spasticity may require a considerable modification in some neurological doctrines regarding the functions of this system. Lassek (100) has completed the eighteenth of a series of detailed studies of the pyramidal tract in which he summarizes 10 years of work on pathological studies in relation to clinical findings in over 12,000 cases suffering from voluntary motor paralysis, 236 of which were studied by himself. He concludes that

> motor paralysis of a chronic nature apparently can occur in man with the pyramidal tract in one of the following conditions: with total, severe, moderate or slight loss of fibers, or with its neurones judged to be in a normal morphological state.

In some patients with chronic complete hemiplegia no demonstrable degenerative lesion of the pyramidal tract could be found. In other cases definite lesions of the pyramidal tract were associated with little deficit in volun-

some of the symptoms may be due to lesions of other systems which either inhibit function of the pyramidal tract or deprive it of afferent fibers playing upon its cells of origin.

Further modification of our conceptions of the functions of the motor cortex in voluntary movement is made necessary by the observations of Welch & Penfield (101) that excision of the sensori-motor cortex in patients with hemiplegia since infancy (and with focal seizures) does not increase the paralysis even though the cortex removed was electrically excitable. In fact voluntary movements were improved largely because of decreased spasticity. Similar observations are reported by Krynauw (102) and Cairns et al. (103) following hemispherectomy.

A supplementary motor area, which may function independently of the

frontal region, on the mesial surface just anterior to the precentral leg area. the contralateral leg, arm, and face are represented in detail, as well as body sensations and more complex movement patterns, such as vocalization, or postural movements involving both arms and head. Arrest of speech and arrest of voluntary movement may also be produced by electrical stimulation. Only temporary speech difficulty and motor deficit with forced grasping occurs following lesions of this area.

associated with unconsciousness [Kaada (86); Liberson *et al.* (122)] In some instances epileptic seizures were produced, even in nonepileptic patients. These findings confirm the new physiological concepts that the amygdaloid-hippocampal complex is concerned in far more than olfactory function.

A firm anatomical and physiological basis for psychosomatic diseases of the gastrointestinal and cardiovascular systems is emerging. The demonstration that repeated functional disturbances of origin within the cerebral cortex may result in structural alterations in the kidney is of particular significance, as the same principle may be found to apply to other organs.

The Epilepsies

A Swedish geneticist, Alstrom (123) has cast a critical eye on the evidence upon which Lennox and his co-workers have previously founded their popularized opinion that heredity plays a major role in the etiology of epilepsy. He finds that much of this evidence is quite insufficient to prove an hereditary basis for seizures. His own investigations on epileptic patients classified as "known, probable, or unknown" as to etiology shows an equally small hereditary factor in each group. We would agree that EEG evidence of "dysrhythmia" in the parents of epileptic patients is not sufficient evidence for heredity of epilepsy, since the incidence of real seizure waves in nonepileptic relatives of patients is extremely rare, even in identical co-twins. Even in patients with so-called "idiopathic" epilepsy, with "petit mal" waves in the EEG, a history of a difficult birth or some form of encephalitis early in life is far more common than a history of seizures in near relatives Nielsen & Courville (124) have found, for example, that there is a higher incidence of "idiopathic" epilepsy in first-born siblings, and suggests that anoxia at birth may play a major role, rather than heredity. At the recent meetings of the American Academy of Pediatrics in Toronto, we reviewed this question and showed that in over 50 per cent of the patients with gross epileptogenic lesions of the brain, verified at operation by Dr. Penfield, the cause of these lesions was unknown, from previous history, and there were no significant neurological signs to suggest an organic lesion of the brain It is obvious, therefore, that the mere failure to find an adequate cause in the history or from the neurological examination does not justify the assumption that there is hereditary basis or even predisposition for seizures. The term "genetic" epilepsy used to describe patients with petit mal or myoclonic attacks is not warranted from a critical review of the evidence which makes it clear that acquired organic disease of the brain (particularly of subcortical structures) may precipitate (at least) these forms of attack *The higher familial incidence of seizures in patients with petit mal* attacks does suggest a greater hereditary predisposition than in patients with other forms of seizure

However, Lennox (125) has since compiled the most extensive study of hereditary factors in 4,231 epileptic patients and 122 pairs of twins with epilepsy, and has treated his data in such a manner as to give a definitive

The factors which contribute toward the postoperative improvement are many, and the cessation of epileptic fits alone as judged from other types of birth injuries treated by cortical excision [Penfield & Livingston (112)] would appear to be a major benefit and may not require such a radical excision.

Lobotomy and Pain

Nonpsychotic patients who were subjected to bilateral leucotomy for relief of pain all showed severe personality disturbances, according to White *et al.* (113, 114). This has even been true in a number of their cases of unilateral leucotomy although not observed by Scarff (115) in his series. White deplores the tendency to substitute bilateral frontal lobotomy for the relief of pain which can be better controlled by cordotomy, sympathectomy, or root section in a high percentage of cases.

Cortical Representation of the Autonomic Nervous System

The importance of the cerebral cortex in the control of gastrointestinal, cardiovascular, and respiratory functions has received renewed support in a series of carefully controlled experimental studies in animals and man. Babkin *et al.* (116, 117, 118) emphasized the inhibitory effects upon gastric motility produced by activation of posterior orbital-anterior insular areas and the anterior cingulate gyrus when animals are maintained under chloralose-urethane anesthesia, all cortical autonomic functions being completely suppressed by barbiturates. Wall & Davis (119), in a series of carefully controlled experiments on monkeys and chimpanzees, have established three separate cortical systems which influence blood pressure and respiration; (*a*) the sensori-motor cortex, (*b*) the posterior orbital-anterior insular system, and (*c*) the temporal-cingulate system. Of particular importance is the convincing demonstration by Hoff *et al.* (120) that excitation of the frontal cortex in the cat produces not only an elevation of blood pressure but results also in pronounced renal cortical ischemia similar to that previously described by Trueta and co-workers in response to peripheral nerve stimulation. The administration of electroshock, as used in psychiatry for electroconvulsive therapy, produced much more marked renal vasomotor effects. With repeated electroconvulsive "treatments" there was produced fatty degeneration of renal tubules.

Autonomic effects have also been obtained from cortical stimulation in man, and although the results are less detailed, they corroborate those produced in animals Chapman *et al.* (121) noted in patients under thiopental (Pentothal; 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate) anesthesia that stimulation of the tip of the temporal lobe produced elevation in systolic and diastolic blood pressure not associated with any consistent changes in respiration. Stimulation behind the temporal tip, however, in the anterior hippocampal gyrus and uncus has resulted in respiratory arrest sometimes

port neurosurgical, electroencephalographic, and direct cortical electrographic studies in relation to pathological findings and results of surgical excision in 68 patients with follow-up studies over a period of 1 to 10 years. Less than one-half of patients with temporal lobe seizures had attacks which might be described as "psychomotor" or "automatism." Over one-half of the patients operated upon were either free of seizures or had had only one attack since operation. Of those operated upon with EEG abnormality restricted to one temporal lobe, and with complete excision of the area of electrocorticographic abnormality, there were over 75 per cent with successful results These findings are similar to the more recent short-term studies reported by Bailey & Gibbs (130) and by Green *et al.* (131). Since about 20 per cent of all epileptic patients have temporal lobe seizures, and over 50 per cent of patients with focal seizures have their site of origin in the temporal lobe, these studies represent a significant advance in our understanding and treatment of epilepsy [see also Lennox (132)] Of special interest are the associated mental disturbances in these patients.

It should not be assumed that all patients with EEG foci in the temporal region, or with seizures consistent with this localization, have cortical epileptogenic lesions in one temporal region. Such lesions may be bilateral, or epileptic discharge may arise in subcortical structures and be projected to the temporal cortex, as shown in the experimental studies of Ajmone-Marsan & Stoll (133) Meyers *et al.* (134) have emphasized again the importance of recognizing that both cortical and subcortical spikes may exist in the EEG of epileptic patients, so that an apparently focal cortical EEG disturbance may be illusory. Some evidence that the thalamus may be involved in the wave and spike of petit mal epilepsy is provided by direct recording from thalamus and cortex in man (80), though reverberating circuits in which both cortical and diencephalic structures interact seems a more plausible hypothesis. Specific forms of disturbance in the EEG in patients with epileptiform disturbances of diencephalic origin are described by Gibbs & Gibbs (135) and confirmed by Stephenson (136) in patients with lesions of the upper brain stem The general importance of ascending reticular projection systems of the brain stem, as well as the specific thalamocortical systems in the origin of epileptiform disturbances in the EEG and in the production of various forms of clinical seizure is just becoming appreciated, as emphasized by Gastaut (137)

Electroencephalography

A most ingenious method whereby the brain waves can be integrated and used to control the depth of anesthesia automatically is described by Bickford (138) and found of practical use in abdominal surgery (139) Pine *et al.* (140) have shown that ACTH and cortisone may improve previously ab-

answer to many of the problems of the heredity of epilepsy. Incidence of epilepsy in all near relatives was only 3.2 per cent, and 3.6 per cent in near relatives of patients without known antecedent brain damage (though many may well have had such, not apparent in history or physical examination). This is three to seven times the incidence in normal population, depending upon the reliability of statistics, which does not argue for a very strong hereditary factor in epilepsy. The evidence from identical twins is more convincing when considering only those with the bilateral wave and spike EEG and with petit mal or grand mal seizures, but even in these cases their parents did not have seizures nor did they have significant abnormality in their EEG. In only 47 per cent of the identical twins did both have chronic seizures, while in dizygotic twins this percentage fell to 2.5 per cent (one case). Lennox concludes wisely that "a genetic factor in epilepsy is probably no greater than it is in many other common diseases."

Confirmation of the Rosenow antibody-antigen skin reaction in idiopathic epilepsy has been affirmed in a careful study of 117 patients with idiopathic epilepsy by Bering (126). There were 78 per cent positive reactions in epileptic patients compared to only 6.7 per cent in control subjects. Patients with known organic cause for seizures were negative with the exception of two cases of posttraumatic epilepsy. Recalling the work of Kopeloff, Barrera & Kopeloff (126a), who have produced experimental seizures by immunological sensitization of the brain, Bering's findings may be of particular significance. They emphasize, at least, the hope that we may soon be able to cast off the "idiopathic" cloak of ignorance in our understanding and management of some of these patients

Kershman *et al.* (127) have presented statistics on EEG and clinical studies in various groups of epileptic patients totalling over 2,600 cases from different parts of Canada. Focal abnormalities occurred in the EEG of over 45 per cent of these cases. Over 80 per cent of those with focal EEG abnormalities had focal cortical seizures as judged by the pattern of onset of their attacks The correspondence would probably have been somewhat higher had a careful analysis of seizure pattern been carried out in all instances. The monograph by Penfield & Kristiansen (128) summarizing the cortical localization in relation to seizure pattern of 259 patients operated upon, with verification of the focus by electrocorticography and electrical stimulation, should be a great aid to clinicians in the establishment of the focus of onset of seizures in many patients which now, unfortunately, are classified as grand mal just because the focal discharge may progress to a generalized seizure.

[illegible] are variously [illegible] notor" has [illegible] confirmed by electroencephalography over 10 years ago, the high incidence and importance of these conditions, and the possibilities of successful surgical treatment are just being appreciated. Penfield, Jasper, and co-workers (129a, 129b) re-

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half showing a suppression of α-activity over the site of the hematoma. Roth (142) has shown that, following electroconvulsive therapy, important abnormalities can be shown in the EEG by light thiopental anesthesia leading to the conclusion that marked changes in the reactivity of the diencephalon must result from electroconvulsive therapy. Cobb & Hill (143) report a distinct form of EEG which seems to characterize subacute progressive encephalitis. Williams & Parsons-Smith (144) have recorded directly from the thalamus in cases of stupor, finding 8 to 12 per sec. spindles, which are interpreted as indicating a disturbance in the ascending reticular system in these states of unconsciousness.

Gastaut (145) has made extensive studies of the use of intermittent photic stimulation, either alone, or in combination with pentylenetetrazol (*Metrazol*), to activate the EEG. Patients with idiopathic epilepsy and those with organic lesions of the diencephalon have low thresholds for myoclonic jerks and bifrontal EEG discharge with this technique. With a method of paired flashes of light separated by different intervals of time, Gastaut *et al.* (146) have studied various parameters of cortical excitability, a technique which appears to have excellent promise in clinical neurophysiology generally.

There have been many other interesting and important studies in this rapidly moving field during the past year, but space forbids their mention here. Of particular note for the practitioner is the publication of the excellent book by Schwab on clinical electroencephalography (147).

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DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY

Hematological Sciences

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INTRODUCTION

In every aspect of hematologic disease in 1950 and 1951, critical biometry has continued to open new vistas of understanding But the apparent untangling of each riddle poses another, and the distance by which the esoteric science outruns the pragmatic art is an inescapable burden on its laboring practitioners

ANEMIAS

Problems in Hemoglobin Synthesis

Iron.—Many details in "ferrikinetics" remain obscure No anomalies in the apoferritin-ferritin system have yet been demonstrated to enter pathological absorption or distribution of iron The dynamics of an iron deficiency may still elude patho-physiological explanation.

Thus, in a study of 20 achyliacs in 100 women between 20 and 60 years (and against expectancy) no statistical differences were found in the hemoglobin levels of the achyliac group [Brunner (1)] Conversely, in 20 young males with "idiopathic hypochromia," 16 had marked acid deficiency [Shorthouse & King (2)] A study of nutritional depression in a rural U. S. population discovered microcytosis in 22 per cent and, surprisingly, macrocytosis in 13 9 per cent of 1200 people, of which, however, only 14 per cent had definite anemia [Youmans *et al* (3)]

Tagged Fe^{55} maternal iron transferred across the placenta facilitates measure of the post-partum accession of iron in the infant. At 18 months only 50 per cent and at two years 70 per cent of the hemoglobin iron was of post-partum acquisition [Smith *et al* (4)] The "ferrikinetics" of radio iron enables some study of erythroid metabolism in a number of conditions. Thus, in polycythemia rubra vera the plasma turnover of iron was increased to five times normal, was reduced after P^{32}, and was lower in secondary polycythemia There was increased turnover in leukemia and pernicious anemia, but it was decreased in a refractory anemia [Huff *et al* (5, 6)]. Reduced marrow activity after I^{131} was similarly demonstrated [Rall *et al* (7)] Radioferrikinetics may prove a diagnostic tool of future import

The cause of abnormal iron storage in hemochromatosis remains obscure. There is familial predisposition, and the process starts early in life [Althausen *et al.* (8)]. The enormous iron deposit was available for hemoglobin

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(*b*) *Vitamin B_{12}*: The earlier studies had obtained two active red pigments from liver (Smith, 1948). It now appears that there are at least four cobalt *pigments of slight chemical, spectral, and microbiological difference*, but undifferentiate activity in animals or man. Vitamin B_{12} is the cyano form of Vitamin B_{12a} (or the identical Vitamin B_{12b}), and the non-cyano Vitamins B_{12c} and B_{12d} are closely related [Smith (22)]. Accumulating studies of clinical effects of the pure individual pigments have revealed no quantitative differences in hematologic or nervous effects in the human [Smith (22); Chalmers (23); Schilling *et al* (24), Watson *et al.* (25); Reid (26); Ungley & Campbell (27)]

It was confirmed that to increase the daily oral mass of pure Vitamin B_{12} *sufficiently produces* adequate responses. At 250 *mg* or below results were irregular [Meyer *et al.* (28, 29)], but higher doses produced full responses [Ungley (30); Carpenter (31)]. In confirmation of previous studies, normal gastric juice led to satisfactory responses when incubated with 10 μg B_{12} [Ungley (30)] *or swine mucosal extracts* [Meyer *et al.* (32)]. Curiously, 1 mg. folic acid together with 10 μg B_{12} (either alone inactive) were synergistically *effective* [*Ritz et al* (33)], *even when administered by separate routes to* eliminate intestinal interaction [Reisner & Wiener (34)]

"Apoerythrin"—*A protein competent to combine with Vitamin* B_{12} termed "apoerythrin" was recovered from normal gastric juice [Ternberg & Eakin (35)] and also saliva [Beerstecher & Altgelt (36)], but its identity with intrinsic factor and the theory that it protects Vitamin B_{12} from intestinal flora was disputed [Spray (37)]

Folinic acid—The "citrovorum factor" (a nutrient essential for leuconostoc citrovorum) may be formed by hydrogenation of formyl folic acid in the presence of ascorbic acid [Hill & Briggs (38)] and was the sole natural form in which folic acid was found in mouse liver, located in the cytoplasm in contrast to the mitochondrial Vitamin B_{12} [Sweinseid *et al.* (39)] Folic acid is converted by the liver in the presence of ascorbic acid into folinic acid [Nichol & Welch (40)], which may explain the importance of ascorbic acid in megaloblastic monkeys [May *et al* (41)] and infants [May *et al.* (42)]. Folinic acid "cured" pernicious anemia in doses similar to the effective doses of folic acid [Jarrold *et al* (43), Davidson & Girdwood (44); Ellison (45); Carpenter (31)], *it also controlled infantile megaloblastosis* [*Woodruff et al* (46)], and was a growth factor for the human infant [Carpenter (31)] It *prevented in mouse leukemia the therapeutic effect of aminopterin* [*Burchenal et al* (47)] and reversed clinical aminopterin toxicity [Schoenbach *et al.* (48)], *thus indicating the mode of action of the* antileukemic amino-folic acids

Other factors.—That such may exist has never lost adherence. Reviewing 45 patients with megaloblastic anemia in pregnancy, 16 of 27 had no assignable dietary cause, 32 of 41 had free gastric hydrochloric acid, and most did not respond to Vitamin B_{12}, but responded to yeast extract in a manner not accounted for by its known folic acid content [Thompson & Ungley (49)]. The authors mentioned the possibility of Lucy Wills factor Owren (50) noted

fabrication if the sufferer was iron starved and repeatedly bled [Beyers & Gitlow (9)].

Vagaries in iron therapeutics attract the continued interest of authors. Iron-carbohydrate complexes are safe for intravenous use in doses up to 200 mg. and are available as Ferrivenin (Britain), Feojectin (United States, made in Britain), Astrafer (Sweden) or Ferrigen (France). These preparations are evidently difficult of fabrication, hence the small number on the market, and preparations other than here named have led to severe encephalopathy with permanent damage [Brich & Till (10)]. Authors have refused decision as to possible dangers of tissue damage [Brown *et al.* (11)] by excessive dosage. Simple iron deficiency responded quantitatively to injected iron in pregnancy [Scott & Govan (12)], as did "simple" hypochromia [Brown *et al.* (11), Horrigan *et al.* (13)], and also the oral-iron resistant hypochromia of steatorrhea [Hawkins *et al.* (14)]. Thirty-eight of 51 patients with hypochromia with rheumatoid arthritis responded, 13 being refractory [Sinclair & Duthie (15)]. Studying the anemia of patients with infection, Kuhns *et al.* (16) found that the characteristic hypoferremia could not be more than temporarily corrected by large doses of intravenous iron; a mean daily rise of 0.035 gm. hemoglobin as contrasted to 0 20 gm per diem in iron deficients was produced; in two autopsied cases 46 per cent and 88 per cent of the iron injected was found in tissues. In patients with cancer the findings were similar [Tötterman (17)] Thus, in a variety of metabolic and toxic diseases iron can be said to be "deviated" to tissues.

First described by Ceelen in 1930, a syndrome characterized by deviation of iron to pulmonary tissues by some cryptic process of local release produces hypochromic anemia with hemoglobin breakdown pigments simulating hemolysis and eventual severe pulmonary siderosis with fibrosis The earlier cases observed concerned children, but a case at 16 to 19 years is instanced [Walton & Williams (18)], and lung puncture was suggested for diagnosis [Ellman & Gee (19)].

Megaloblastic degeneration.—In the synthesis of nucleoproteins, any deficiency in the substrates or anabolic enzymes which serve the reaction uracil→thymine (5 methyluracil)→thymidine (desoxyribothymine) produces as its morphologically identifying feature the Ehrlich megaloblast That similar deficiencies must occur in the cytidine and in the purine (guanidine and adenosine) nucleotide synthesis seems logical, but at this time, lacking a *morphologic* clue, such cannot be recognized Failures of ingestion, absorption, or production of the various factors concerned are the known modes by which megaloblastic degeneration is caused. The exact role of these factors in thymidine synthesis is not clear, and evidences from clinical or bioexperimental fields often appear contradictory. The following is a superficial abbreviation of some of the points of discussion in the evolution of our knowledge in 1950 and 1951.

(*a*) The current clinical status of the pernicious anemia-megaloblastic anemia problems was fully reviewed by two authorities [Castle (20), Witts (21)].

Further instances of symptomatic hemolytic anemia have been reported in lupus erythematosus [Dubois (75); Lee *et al.* (76)] Its incidence appears to be about three to four per cent in lupus. In a case of congenital porphyria, splenectomy benefited hemolytic anemia and led to disappearance of excess erythrocytic coproporphyrin I and uroporphyrin I [Aldrich *et al.* (77)]. The anemia of leukemia was identified as hemolytic by the Ashby technique [Ross *et al.* (78); Berlin (79)]. Severe hemolytic anemia has complicated eclampsia [Kistner & Assali (80)], teratoma and caseous tuberculosis [Lindeboom (81)], infectious mononucleosis [Sawitsky *et al* (82)], and atypical pneumonia [Neely *et al.* (83)] Two instances of chronic hemolytic anemia with cells susceptible to both cold and acid were believed therefore different from the Donath Lansteiner and Macia Fava diseases [Liu (84)]. An unusual form of chronic hemolytic anemia, congenital but non-familial and non-spherocytic, in a 27-year-old Negro, was believed similar to the previous description of Haden [Feinberg & Watson (85)]

In two families with congenital microspherocytosis, epidemic crises have been observed, chills and fever marked the onset, and an extrinsic cause appeared likely [Marson *et al* (86), Li *et al.* (87)]. In an autopsied case of Macia Fava syndrome attention was again drawn to the frequency of thrombosis [Ellenhorn *et al.* (88)].

Iso-immunization—The "blood groups," i.e., the genetically inherited red cell protein systems which may give rise to transplacental or to transfusion antibody hemolysis, will always remain a specialized, complex field Progress was recorded in studies of P-p [Hennigsen (89)], JK[a] [Race *et al.* (90)], Kell-Cellano [Cochrane *et al.* (91)], Lewis-X [Andresen & Hennigsen (92)], the "Duffy" [Cutbush *et al.* (93), James & Plant (94)] systems In the M-N-S-O- system, anti-S antibodies may apparently develop spontaneously [Coombs *et al* (95)] or in first pregnancy [Jacobowitz *et al.* (96)], similar to anti-A [Zontendyk & Broido (97)]. An individual containing genotype -D-/-D- [Race *et al.* (98)] was the curious product of cousin marriage. A recipient with a "collagen disease" developed six differentiated antibodies in three transfusions [Waller & Race (99)].

Rh negative fetuses did not produce an "anamnestic" rise in Rh antibody titer in 11 mothers [Wiener *et al* (100)]. Transplacental antibodies (Rh) had a half life of 30 days in the infant, but a and b agglutinins were rapidly lost [Wiener (101)] Seventy per cent of 23 Rh negative recipients receiving in all 184 transfusions of Rh positive blood were sensitized to maximum titer of 1:2084, however, no severe hemolytic reactions were seen [Klein *et al.* (102)].

It was concluded that transplacental ABO, or Rh-Hr antibodies, were not and *univalent coldfixed (incomplete) maternal "autoantibodies" were postulated* to be the cause of physiologic icterus neonatorum [Wexler & Wiener (103)] Contrary to belief, it was denied that normal neonatal hemolysis occurs [Langley (104)] In erythroblastosis fetalis more pleas were made for exchange transfusion [Brancato (105), Agerty *et al* (106)], and the theoretical wisdom of using packed red cells, thus avoiding transfused adult con-

that even after full response to Vitamin B_{12} or folic acid, cases of pernicious anemia remain macrocytic and hypoprothrombinemic, and retain abnormal (fetal) hemoglobin. The "curative" factor has been purified from liver (Laland, Nyegaard and Co.) and called "Protein Synthesis Factor."

Biological interrelationships.—Curious biological interrelationships between megaloblastic anemias and both antibiotics and ketosteroids remain unexplained Aureomycin can produce a sharp reticulocytosis in pernicious anemia [Lichtman *et al.* (51)], probably by the alteration of intestinal flora [Davis & Chow (52)]. However, such a mechanism would not explain the observed recovery of two cases of megaloblastic anemia of pregnancy after massive parenteral penicillin G [Foy *et al.* (53, 54)].

Miscellaneous data.—The onset of pernicious anemia in four juveniles in an excellent study was shown to demonstrate anemia some years prior to achylia [Reisner *et al.* (55)]. The increasing frequency of subacute combined degeneration of the cord without anemia was attributed to the use of vitamin tablets containing folic acid [Conley & Krevans (56)]. In 34 of 95 cases of fish tapeworm anemia, severe subacute combined degeneration occurred, matching the incidence in pernicious anemia [Bjorkenheim (57)]. Vitamin B_{12} alleviated nutritional neuropathy [Bean *et al.* (58)].

Electroencephalographic studies indicated neurologic changes in pernicious anemia as not due solely to anemia [Samson *et al* (59)]. Early diagnosis of subacute combined degeneration may be aided by gastric biopsy using Woods' biopsy tube [Doig *et al.* (60)]. Marrow cultures indicated that a toxic factor may be present in the serum of pernicious anemia [Thompson (61), Lathja (62)].

Problems in Abnormal Blood Destruction

Scholarly reviews of certain hemolytic mechanisms [Ponder (63)] and destruction of red corpuscles [Wasastjerna (64)] are valued contributions. The mechanism of *experimental* hemolysis produced by agglutinins (e.g., as after incompatible transfusion) was explained as due to lytic tissue substances produced by vascular injury in the region of cellular agglutination [Castle *et al* (65)] The electron microscope has discerned surface changes on red cells in chronic hemolytic anemia [Matthes *et al* (66)].

The Coombs' test may give a false negative in undiluted titers due to the prozone effect [van Loghem *et al* (67)] Various saline agglutinins and a number of incomplete antibodies have given negative direct and indirect Coombs' tests [Rosenfeld *et al* (68)] Sporadic positive tests have occurred in pernicious anemia [S [illegible] [Meacham *et al* (7 [illegible] were used together [illegible] congenital microspherocytosis (against previous experience), thalassemia, idiopathic thrombocytopenic purpura, and myelomas as well as customarily in acquired hemolytic anemia [Wright *et al* (72, 73)]. Incomplete forms of cold autoantibodies were demonstrated in normal serum [Dacie (74)].

Sicklemia in non-Negro peoples has hitherto been dismissed as due to admixtures, but the discovery of seven per cent sicklemics (moist stasis method) in Yemenite Jews, a largely Semitic people, rivals that in the American Negro and postulates a new genetic focus [Dreyfuss & Benyesch (126)].

It was again noted that sickle cell vascular symptoms can occur in the absence of anemia [Green & Conley (127)] and that the anemia may be caused by a number of pathologic mechanisms [Singer *et al* (128)]. Altitude may produce crisis [Sullivan (129)].

Thalassemia —Cooley's anemia has similarly received some esoteric investigation Varying proportions up to 50 per cent of the total have been identified as "fetal" hemoglobin [Liquori (130); Astaldi *et al.* (131); Singer *et al* (122)]. Despite the high body iron content, the iron avidity by balance studies was not excessive [Hamilton & Fowler (132)]. Correction of the low level of iron-binding protein by injection of up to 20 gm thereof did not influence the anemia [Sisson *et al.* (133)] A neonatal study observed 4 05 M rbc/cu. mm with 12 7 gm hemoglobin per 100 cc at 85 days, and anemic death at 165 days [Banton (134)]. (Possibly the mother can contribute the missing enzymes) Positive Coombs' tests have been observed in thalassemia [Wright *et al* (73)], perhaps some clue to the clinically noted evidences of hemolysis. How this fits into the concept of defective hemoglobin manufacture is not clear.

The Cooley syndrome is of far wider distribution than its Mediterranean focus, just as Caminopetros (who it is generally forgotten locally was first to publish genealogies of this disease and to note the compensatory polycythemia in the carrier) had suggested in 1937 that it might be. Instances are noted in Chinese [Silver (135)], Mexican [Silver (135)], Maltese [Mooney (136)], American Indian [Prouty (137)], American Negro [Dagradie *et al* (138)], Sinhalese [Silva & Weeratunge (139)], Filipino [Stransky & Regala (140)], Sino-Filipino [Carpenter (31)], and Filipino-French [Silver (135)].

Miscellaneous Anemias

Refractory anemias of indeterminate origin with or without marrow pathology are not rare, but since they do not collate well, many go unrecorded.

A further plea was offered for consideration of the enigmatic osteosclerotic myelofibrosis as due to disoriented differentiation of pre-hemopoietic cells [Munk (141)] Four cases of fatal hyperchromatic anemia with anomalous erythroid reversionary changes without obvious cause are explained as "erythromyelosis," or "erythroleukemia" [Ludin (142)] Four children were observed over 7 to 11 years with "stationary hypoplastic anemia " The anemia was commonly macrocytic, starting in the first year of life, marked by severe reduction in marrow erythropoiesis, with high serum iron and without thrombocytopenic hemorrhage. There was mental retardation in some [Palmen & Vahlquist (143)]. Another case of Fanconi's anemia in a child with the characteristic leukopenia, thrombopenia, cutaneous pigmentation, and bony malformities was described [Beautyman (144)]

Idiopathic steatorrhea may cause either a resistant iron-deficiency anemia

glutinin, was advocated [Wiener & Wexler (107)]. It was further claimed that exchange transfusion caused a "decrease in mortality along with marked reduction in incidence of kernicterus" [Diamond *et al.* (108); Allen *et al.* (109)]. In the causality of kernicterus, prematurity, infections, and factors other than hemolytic antibodies were causative in one-third to one-half of the instances [Zuelzer & Mudgett (110); Gerrard (111)] The conclusion that prevention of kernicterus was lowered from 25 per cent to 2 per cent by exchange transfusions with blood from female donors [Diamond & Allen (112)] has been severely criticized. The reduction of infant mortality from 37 per cent before 1947 to 3 per cent in 1947 to 1950 was due in part to over-all reduction in the severity of cases by parental knowledge of the Rh factors, and not to exchange transfusion as employed in the latter three years [Mollison & Cutbush (113)]. The hemoglobin concentration in the infant cord blood was closely related to the survival chance in exchanged infants, the MD/50 being 8.09 gm.; and infants with positive direct Coombs' tests but hemoglobin over 15.5 gm. per 100 cc have a one chance in twelve of kernicterus [Mollison & Cutbush (113)].

GENETIC ANEMIAS

Sickle cell disease.—Sickle cell phenomena engendered distinguished esoteric studies centering on the abnormal hemoglobin. The differences were said to involve the globin complex. Reduced sickle cell hemoglobin in phosphate buffer is only 1/100 as soluble as "oxysicklehemoglobin" and reduced sickle cells showed crystalline properties in polarized light [Perutz & Mitchison (114), Perutz *et al.* (115)] The sickle cell was conceived as a "hemoglobin tactoid thinly veiled by a somewhat distorted cell membrane" [Singer (116)] The sickle hemoglobin contained three moles of sulfhydryl/mol. hemolgobin, whereas normal hemoglobin contained only 2 moles sulfhydryl/mol. hemoglobin [Kass *et al.* (117)] Crisis in two sicklemics given corticotropin (ACTH) was possibly due to concomitant changes in glutathione levels produced thereby [Kass *et al.* (117)] and the *in vitro* prevention of sickling by Hg^{++}, As^{++} or iodoacetate was possibly due to their sulfhydryl inhibiting properties [Ingbar & Kass (118)] Abnormal electrophoretic CO-hemoglobin motilities have been demonstrated in lower proportion in sickle cell trait (23 to 45 per cent) and higher proportion in sickle cell anemia (76 to 98 per cent) [Pauling *et al.* (119), Bowers & James (120); Wells & Itano (121)], and the proportion of sickle-hemoglobin has been deduced from alkali denaturation rates [Singer *et al* (122)]

In a study of 75 sicklemic kindreds the monozygous-bizygous inheritance was held to determine the fact of trait or disease [Neel (123)]. However, in African Negroes the ratio of sicklers to anemics was less than 1:1000 [Raper (124)], whereas the incidence of sicklemics approached 30 per cent in certain Nilote tribes [Lehmann (125)] This introduced the necessity for another factor than homozygosity alone in causing anemia Genetic penetration is not independent of other genetic properties, and a factor involving European inheritance is postulated

been exposed to potentially noxious agents, all had normal marrows, and one did not benefit by splenectomy [Adams & Witts (163)]. Evidences of intravascular destruction of granulocytes by "reticulocytes" was seen in one case for a short time [Heckner (164)]

Infectious mononucleosis—Subclinical epidemic infectious mononucleosis is suspected to occur Five of 26 isolated men had the clinical disease; one only had a positive heterophil reaction; all 26 had abnormal cells [Goldthwait & Eliot (165)]. In an epidemic in a student class, 51 of 102 men showed some evidence of infectious mononucleosis, 33 of 51 having positive thymol turbidity, of which seven were still positive after 22 months [Watson *et al.* (166)]. A 24-year-old male developed progressive cirrhosis in three years after an illness diagnosed as infectious mononucleosis, with heterophil titer of 1:800. (The characteristic infectious mononucleosis blood picture was not described and the heterophil was not absorbed) [Liebowitz & Brody (167)]. In a converse study of interest, 20 per cent of diagnosed infectious hepatitis showed heterophil titers over 1:56, highest 1:448; in seven there were Forssman antibodies, five had both types as in the normal, and one had the infectious mononucleosis type of antibody by absorption study [Liebowitz (168)] Hematuria may mark the onset of infectious mononucleosis [Thompson & Pitt (169)] In 34 patients historically reported as showing neurologic involvement, 14 have been meningitic, 9 encephalitic, 6 peripheral, and 7 mixed peripheral-encephalopathic neuropathies Eighty-five per cent recovered without sequel, but the cerebro spinal fluid changes may persist [Bernstein & Wolff (170)] Penicillin was useless in 166 cases [Bennicke (171)], but mixed reports for aureomycin [Burnett & Milne (172), Carter & Sydenstricker (173)] were accompanied by claim for the limitation of oral and pulmonary secondary manifestations [Cronk (174)]. Finally, it was alleged that the "specific" cell of infectious mononucleosis is a "virocyte" to be found in a number of viral diseases [Litwins & Liebowitz (175)]. Acute infectious lymphocytosis may occur in an adult [Malamos & Stamatelakis (176)].

Leukotic Disorders

Etiologic considerations—Familial leukosis involved five of eight siblings, two lymphatic, two reticuloendotheliosis, and one with anemic monocytosis unautopsied [Anderson (177)] Congenital leukosis, twice myeloid [Pein & Garvie (178), Taylor & Geppert (179)], once lymphoid [Heen (180)], can be added to the series, dominantly myeloid, previously collated (Cross, 1944). Over the 20 years studied, the incidence of leukosis in radiologists was nine times as great as in all physicians [March (181)], a disparity probably not resulting from better diagnosis only.

Pathogenesis—Guinea pigs ten days after intraperitoneal injection of leukemic plasma developed a uniform syndrome of anemia, hair loss, and death with histocytic proliferation and hemolysis, the agent was passaged, was time-stable when frozen, and similar results were not obtained with control plasma from a number of diseases [Magrassi *et al* (182)] From Hodgkins

[Hawkins *et al.* (14)] or a refractory hyperchromatic macrocytic anemia and potentially the so-called Looser-Milkman osteomalacic syndrome [Anderson (145)].

Severe anemia (2.2 M rbc/cu. mm.) lasting eight years with irregular fever, terminal splenomegaly, leukopenia, useless splenectomy, and death after 108 transfusions was characterized by "owls eye" cytomegalic inclusion disease in the liver cells and elsewhere. (This disorder may be akin to the inclusion body disease which produces a pseudo-erythroblastosis fetalis and neonatal death) [Wyatt *et al.* (146)]

The anemia of advanced cancer is in no way related to the distribution of osseous metastases [Shen & Homburger (147)]. Eleven of 40 patients after radical gastrectomy developed macrocytic normoblastosis, and the defective post gastrectomy fat absorption was pointed out as a possible factor [Brain & Stammers (148)].

Blood Reactions Due to Drugs and Chemicals

For every hematologic reaction to a drug which reaches the literature there are many unreported and unrecognized Short experimental series of observations are without value in measuring the frequency or severity of reactions. This discussion does not list all reported reactions

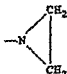
Fatal aplastic anemia was reported after approximately 35 gm of chloramphenicol [Rich *et al.* (149)], and further has been observed in three cases after small doses taken together with chlorprophenpyridamine (Chlortrimeton) in two and thonzylamine (Neohetramine) in the third for mild upper respiratory infections [Carpenter (31)] Other reports are known to be under
followed
in); or
to the
cemide
(Phenurone) [Simpson *et al* (152)]. A list of other recently described causes is offered [Boon & Walton (153)] *Hemolytic anemia has been caused by* diphenhydramine (Benadryl) in three instances [Crumbley (154)].

Agranulocytosis has been repeatedly recognized after antihistaminics,
Cahan
zamine
oxazole
Massie
(161)] have also been implicated, and in a neutropenia caused by mercurials dimercaprol (BAL) was followed by complete recovery in five days [Bender *et al.* (162)].

White Cell Reactions

Granulocytopenia.—Apart from acute drug reactions, chronic agranulocytosis may be a diagnostic problem. Five patients (four female) were observed over two to ten years with hypogranulocytosis, all had previously

diseases, rheumatoid arthritis, asthma and psoriasis [Diaz (201)], and in glomerulonephritis The attack on regional tumors with intraarterial HN_2 caused the accustomed general hematologic responses [Bateman *et al.* (202)]. B-naphthyl-di-2-chloroethylamine ("R 48") was used orally in doses of 3 to 400 mg. daily, with responses that were slower and more easily controlled than with HN_2 [Matthews (203)], but were on the whole inferior to HN_2 [Gardikas & Wilkinson (204)] *Triethylene melamine, a complex containing*



three active complexes was successfully used with results similar to those from HN_2 in doses of 0.12 to 0.20 mg./kg. I.V. or 2 5 to 10 0 mg /day per os [Karnofsky *et al.* (205)]. This group has tested a number of its congeners in mouse leukosis [Burchenal *et al* (206)].

Aminopterin.—The prevention of conversion of folic acid to folinic acid by amino substituted pteroylglutamic acid is discussed under "folic acid" above Studies on aminopterin resistant AK4R leukemia in mice indicated the tumor resists all 4-amino derivatives but not 9-methyl folic, crude x-methyl folic or 2-6 diaminopurine, with the conclusion that alternative metabolic pathways bypass the folinic acid system [Burchenal & Kingsley-Pillers (207)]. Such studies indicated the futility of turning to another 4-amino complex when clinical leukemia becomes aminopterin resistant. The year's reports on adult leukemic series treated with the aminopterin group were not encouraging [Meyer *et al* (208); Dacie *et al* (209); Meyer & Newman (210), Sacks *et al.* (211)].

Urethane—The toxicity of acetyl-carbamide is emphasized in the report of a case of hepatic necrosis; culled from the literature are four cases of pneumonia without leukocytosis, two cases of marrow aplasia, and one of agranulocytosis [Ohler *et al.* (212)]. In mice urethane produced pulmonary adenomatosis, glomerular and genital lesions [Mostofi & Larsen (213)]

Radiation.—In patients treated with P^{32} or Y^{90} the peripheral improvement in lymphatic leukemia was often not matched by the marrow improvement [Berlin & Lawrence (214)] A method of securing far more critical quantitative application of radiation therapy [Osgood (215)] appears to be good sense

Polycythemia and Erythromyelosis

In the mouse, transferrable luteomas produced an endocrine polycythemia, not yet paralleled in human symptomatic polycythemia [Gottschalk & Furth (216)]. Two patients with polycythemia due to pulmonary arteriovenous aneurysms were reported [Armentrout & Underwood (217)]. Both had familial hemorrhagic telangiectases which were said to be present in

tissue an agent which would fix the serum complement of patients was passaged in eggs [Lundbäck & Löfgren (183)]. French observers saw pathologic intracellular bodies in leukemic leukoblasts by electron microscopy [Chevallier (184); Bessis (185); Oberling *et al* (186)]. Cross circulation between humans variously disordered indicated the importance of the pulmonary bed in removal of leucocytes, and in three of seven studies the leukemic participant underwent marked decrease in the count [Bierman *et al.* (187)], with some suggestion that the role of the pulmonary bed might determine the nature of the leukemia.

Course—In a careful study of remissions in 300 leukemic children, spontaneous remissions, of which 4.4 per cent were "complete," averaged 10 weeks with duration of post-remission life 29.7 weeks Severe infections, cured by antibiotics, were an evident factor in induction of remissions [Diamond & Luhby (188)]. The importance of these as baseline figures in the evaluation of antileukemic therapy is obvious (*vide infra*).

Clinical observations—Leukemic anemia was proved hemolytic despite no hyperbilirubinemia [Ross *et al.* (78)]. In a woman with chronic myeloid leukemia, severe refractory hypochromic anemia and intense marrow normoblastosis eluded explanation despite detailed study [Young *et al* (189)] The frequency of bone pathology and the scurvy-like epiphyseal change in leukemic children was well illustrated [Dresner (190)]. Acute renal failure was reported as an uncommon manifest of cryptogenous monocytic leukemia [Taylor *et al.* (191)] and in another leukemic was due to uric acid renal block after tri-ethylene melamine [Kravitz *et al.* (192)] In 15 patients with myeloma, functional studies showed no specific renal lesion, both glomerular filtration rate and tubular secretory capacity being reduced [Armstrong (193)]. As in other renal lesions, in myeloma kidney disease low serum potassium levels may be found [Carpenter (31)], a factor of importance if use of ACTH is considered

Duplication of reticuloses in a single patient is not as exceedingly rare as published combinations might indicate Recent reports associated multiple myeloma and polycythemia [Lawrence & Rosenthal (194)], lymphatic leukemia and Hodgkins disease [Seife *et al.* (195)]. The status of a lymphocytic leukemoid reaction with profound blood and marrow lymphocytosis accompanying disseminate mammary cancer must be questioned as a duplex neoplasia despite the lack of lymphatic infiltration at autopsy [Kleeman (196)]

Therapy of Leukotic Diseases (Excluding Hormonal)

A review titled "Present status of clinical chemotherapy" was ably presented [Karnovsky & Burchenal (197)].

Mustards.—Terminal publications on large series of dichloroethylamine amines (nitrogen mustards; HN_2) are available [Spurr *et al* (198); Bauer & Erf (199); Alpert *et al* (200)], emphasizing previous conclusions. Of interest is the recognition of the ability of HN_2 to produce ACTH-like effects probably by pituitary stimulation and a consequent use for HN_2 in the "dysreaction"

Owren, which, however, have since been further developed. In recent contributions by Owren (231) the consumption-conversion dynamics of all the known factors were studied in completely controlled systems. He holds (with Quick, 1947) that the reactions are strictly stoichiometric and not autocatalytic, as has been held [Milstone (229), Stefanini (232)] His schema of coagulation is unavailable in Stefanini's review and is therefore presented.

Schema I (a) antihemophiliacglobulin+platelets→thromboplastin
(b) thromboplastin+proconvertin+Ca→convertin (Factor VII)

Schema II (a) convertin+prothrombin→thrombin
(b) proaccelerin+thrombin→accelerin (Factor V)
(c) accelerin+prothrombin→thrombin

COAGULATION FACTORS

Antihemophiliac globulin and hemophilia—It is generally held that deficiency in *antihemophiliac globulin is the cause of hemophilia. It has been also called thromboplastinogen* [Quick (233)] Its interaction with platelet factors is held [Owren (231)] to release active thromboplastin. However, its key position in hemophilia has been questioned, it being held that when diluted severely, hemophiliac blood will coagulate exactly as normal, and that by suitable methods of dilute extraction hemophiliac blood will deliver as much antihemophiliac globulin as similarly treated normals [Tocantins *et al* (234)] The normal presence of a dilutable anti-first phase substance was propounded [Fiala (235)]. A single instance was reported of a hemophiliac possessing a recoverable coagulation retarding agent, thermostable and not heparinoid, antithromboplastic, or antithrombin, and not an antibody [van Creveld *et al* (236)] *By two-stage methods the prothrombin was often reduced in hemophiliacs when normal by the one-stage procedure* [de Vries *et al* (237)] The prothrombin consumption test is promoted as an ancillary diagnostic aid [Quick & Favre-Gilly (238); Soulier (239)], but the consumption may clearly be reduced by defects other than hemophilia and is influenced by a composite of accelerating factors [Stefanini & Crosby (240)]

Hemophiliac hemorrhagic disease may be found in members of hemophiliac inheritance who have no prolongation of coagulation time [Merskey (241)], and a hemophiliac father mated to a carrier female bred a laboratory tested hemophiliac girl [Israels *et al* (242)] Critical methods reveal defects in *the proconvertin→convertin dynamics* in the carrier female [Owren (231)]. It was claimed that *ergot alkaloids shorten the hemophiliac coagulation to* normal [Vodopivec & Jelavic (243)]

The alleged defect in the platelet utilization factor in hemophilia (Brinkhaus) appears not yet supported, but since thrombin has a marked lytic effect on platelets [Stefanini (232)], the lytic property of normal serum can be explained.

Calcium.—Studies of quantitative decalcification of siliconized blood on

over 50 per cent of such aneurysms [Goldman (218)]. The accurate blood volume determinable by P^{32}-labelled cells did not provide a reliable means of dividing primary from symptomatic polycythemia and indicated the hematocrit is often falsely high by virtue of a low plasma volume [Berlin *et al.* (219)]. The relationship of polycythemia rubra vera to leukemia was critically examined and of the 30 instances published, 25 had previous irradiation, believed causally significant [Schwartz & Ehrlich (220)]. Though competent to produce remissions, nitrogen mustard was rejected as a suitable therapy [Shulfenberger & Watkins (221)]. Eighty per cent of 108 patients responded successfully to P^{32} [Wiseman *et al.* (222)]. The death pattern of 32 patients not treated with P^{32} was compared with 27 who received it. In each series about one-third suffered thrombosis, and one-fourth had leukemia or other malignant diseases, the series possibly being too short to develop any significant differences. Evidently in both the treated and untreated, vascular accidents were the greatest danger [Stroebel *et al.* (223)].

Bone Marrow

"Neither the gross appearance nor the total nucleate count of the marrow aspirate fluid is a reliable estimate of the bone marrow cellularity" [Fadem & Berlin (224)] Accordingly, histological particle preparations may be of exceeding importance, as long since stated by Schleicher. In most aspirations these can be prepared with ridiculous ease [Carpenter (31)]. Using a specialized section method the marrow granuloma of brucellosis was again demonstrated [Fisher (225)]. The significance of mast cells as evidence of hypoplasia was emphasized [Fadem (226)]. In 5 of 100 instances of disseminate malignancy the bone marrow gave the first knowledge thereof [Rubinstein & Smellin (227)].

HOMEOSTASIS

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The essential brevity of these pages precludes any detailed examination of the data presented since 1943, and readers are referred to such reviews as those of Owren (228), Milstone (229), and Stefanini (230) The last author presents schematically the theories according to Quick, to Ware, Guest & [illegible] particular reference to accelerators, [illegible] correlate the various "factors" as [illegible] also presents the earlier views of

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system is sharply reduced together with prothrombin by bishydroxycoumarin (Dicoumarol) [Mann *et al.* (260), Owren (231), Koller *et al.* (262)] and by operation [Warren & Belko (263)]. It may be missing congenitally [Alexander *et al.* (247)].

Thrombin and fibrinogen.—The action of thrombin on fibrinogen is proteolytic, releasing three per cent of the protein as L-aminoglycine rich peptide [Bailey *et al.* (264), Lorand (265)]. The reaction velocity depended on fibrinogen and thrombin concentration, pH, ionic strength, and presence of various inhibitive additives, such as gum acacia, urea, or phenols. Thus, accelerators do not necessarily act directly on the clotting mechanism [Waugh & Livingstone (266)]. The unitary nature of fibrinogen has been questioned, components A and B varying in certain disease states [Crumrine & Lyons (267)]. The clotting of fibrinogen by staphylocoagulase needs plasma cofactors other than those concerned with the thrombin precursor mechanisms [Tager & Dodge (268)].

ANTICOAGULANTS

It is believed that any one of the "factors" involved in blood coagulation may have a specific inhibitor [Owren (231)] Only some of these have been properly identified in disease and for the most part the specific site of action is unidentified

A non-specific thermolabile albumen in complex with prothrombin is recoverable at two µg /cc. from all plasmas and inhibits recalcified plasma coagulation This effect can be lost by dilution [Fiala (235)]

A theory for the action of heparin postulates the release of a lipoid coagulation inhibitor from a bound form [Applezweig *et al.* (269)] The marked reduction of lipoid chylomicrons (as originally obverted by Hahn) and on lipoprotein macromolecules (Sf 10–20) indicated the possible significance of heparin in lipoid metabolism [Graham *et al.* (270)]. The effect fails *in vitro* indicating the existence of co-factors as in blood coagulation Microparticulate heparin in oil maintained effective concentrations for 28 hours after injection of 400 mg [Wald *et al.* (271)]. The concentration of heparin required to prolong the coagulation time varied directly with the platelet count, and "heparin tolerance" was not a measure of circulating thromboplastin [Hartman *et al.* (273)]. The synthetic polysulfuric carbohydrate ester "paritol" produced satisfactorily long coagulation time in doses of 35 to 37 mg /kg. I V. maximal in one-half to one hour, duration eight hours [Sorensen & Wright (274), Chapman & Ory (275)] Low molecular weight dextrans (mol wt 20000) are sulfonated polysaccharides having heparinoid action and may be so used, and require the serum heparin co-factor [Walton (276)]

In an acute hemorrhagic diathesis prothrombin time with human brain thromboplastin was measured as 14 per cent, but with rabbit brain, 100 per cent, stated due to species specific antithromboplastinemia [Stohlman *et al* (277)] In acute pancreatitis, 92 per cent were said to have a diagnostic increase in antithrombin titers for 72 hours [Innerfeld *et al* (278)]. Idiopathic

Amberlite suggested that active calcium is protein bound and not ionized [Stefanini (244)]. Calcium was essential for the lysis of platelets by thrombin [Stefanini (244)]

Proaccelerin [*Owren* (231)].—Synonyms: "Labile factor" (Quick), "Factor V" (Owren), "Plasma accelerator globulin" (Ware & Seegers), "accelerator factor" (Fantl & Nance), thrombogéne (Nolf). [For synonym references see Stefanini (230)]

This substance is converted by thrombin to accelerin [synonyms: serum accelerator globulin (Ware *et al.*), Factor VI (Owren), propriété excito-productrice de la thrombine du sérum (Bordet)]. Accelerin hastens the conversion of prothrombin to thrombin and is quantitatively consumed in the process (Owren).

Congenital defects in Factor V (proaccelerin), a syndrome originally named parahemophilia by Owren, were further instanced as the cause of hemorrhagic diathesis on a congenital basis [de Vries *et al.* (245); Frank *et al.* (246); Alexander *et al.* (247)]. In a purpura fulminans after scarlet fever the factor was critically defective in two cases. One case was saved by exchange transfusion; the other had an associated heparinoid antithrombin present [Koller *et al* (248)] A patient on propylthiouracil developed prolonged clot and prothrombin times due to Factor V defect and was cured by discontinuance of the drug and a homologous plasma infusion [Craddock *et al.* (249)] Proaccelerin is not much affected by bishydroxycoumarin (Dicoumarol), but falls in liver disease about as prothrombin It is never reduced in obstructive icterus [Owren (250), Stefanini (251)].

Prothrombin.—It has been suggested in the past two years [Quick and Stefanini (252)] that prothrombin ("Prothrombin A") exists partly free and partly as an inactive precursor termed prothrombinogen [Hartmann *et al.* (253)] exhibiting quantitative species differences [Quick & Hussey (254)] It was theorized that one accelerator was derived from prothrombin breakdown [Alexander *et al.* (255)]. Conversion of prothrombin to thrombin was said to consist of more than a single step [Seegers *et al.* (256)]. Congenital absence of true prothrombin was seen in a five-weeks-old infant whose brother was likewise afflicted [Landwehr *et al.* (257)]

"Convertin" (*Owren*).—Synonyms: "Factor VII" (Owren, 1949), "co-thromboplastin" (Mann & Hurn, 1949), "thrombogene" (Nolf), "serum prothrombin conversion accelerator or SPCA" (Alexander *et al*). [For synonym references see Stefanini (230).]

This factor was effectively determined in 1949 It is believed to be a co-factor to thromboplastin [Mann & Hurn (258, 259)]. Owren (231) believes it is the prime effective convertor of prothrombin and that it exists in precursor inactivity as "proconvertin " He has shown charts indicating the quantitative conversion of proconvertin to convertin by thromboplastin There is supporting evidence for such a conversion by platelets [Mann *et al.* (260, 261)]. The existence of a precursor to "serum prothrombin conversion accelerator" has been suggested [Alexander *et al.* (247)]. It is shown that the

system is sharply reduced together with prothrombin by bishydroxycoumarin (Dicoumarol) [Mann *et al.* (260), Owren (231), Koller *et al* (262)] and by operation [Warren & Belko (263)] It may be missing congenitally [Alexander *et al.* (247)].

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hyperheparinemia (23 μg./100 cc.) fell to 2 μg./100 cc. after 25 mg. of desoxycorticosterone acetate in four days, relapsing 72 hours after cessation [Bell & Stuart (279)].

Bishydroxycoumarin (Dicoumarol).—Eighty deaths have been attributed to anticoagulants in the literature (280). In a series of 9,609 patients, 1.9 per cent had major hemorrhage [Nichol (281)]. A single dose, 300 mg., extended initial 20 second times to 172 seconds in an azotemic patient with periarteritis [Butler & James (282)]. Death followed customary dosage in two patients with congestive failure [Powers (283)]. Malingering hemorrhage was induced by a patient [Stafne & Moe (284)]. Repetitive pulmonary embolism from intramural thrombi was successfully treated over 51 months [Rice *et al.* (285)] In reversing bishydroxycoumarin, Vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) is more rapid than menadione [Watkin *et al.* (286)] and is active in ratio approximately 100:1, probably by mutual competition for an epoenzyme essential for prothrombin fabrication [Collentine & Quick (287)].

Effective substitutes with sundry quoted advantages over bis-hydroxycoumarin are 2-phenylindane-1,3-dione (200 mg./day) [Jaques *et al.* (288); Bjerkelund (289)]. Cyclocoumarol (2 mg./kg.) [Scheel (290)], 4-hydroxycoumarin (#63) (2 mg./kg.) [Rotter & Meyer (291)], 4,4'-dihydroxydicumaryl ethyl acetate (600 to 900 mg./day) [Burke & Wright (292)]. However, the current problem in coumarin therapy is not to find a more smoothly operating drug, but instead a better mensuration than the standard Quick one-stage technique The activity of this test depends on the convertin and accelerin systems as well as prothrombin content, and as generally performed cannot be expected to measure anything in particular.

Vascular Consideration

Non-thrombocytopenic purpura.—Penicillin in three instances [Crisp & Cohen (293)] and mentholated cigarettes [Highsten & Zeligman (294)] were instanced as sensitizing agents in purpura The import of meningococcal septicemia was emphasized in children [Dunn (295)] and from two cases of [illegible]-Henoch purpura pleuro-pneumonia-like organisms have been cul-

rated

able

than

simple local hemorrhage [Balf (297)]

Thrombocytopenic purpura.—The pathologic life of the platelet received further attention. Transfusion of silicone preserved platelets into non-productive thrombocytopenics indicated survival times of four to eight days, whereas, in idiopathic thrombocytopenic purpura and in splenomegalic thrombocytopenic purpura the platelet survival was 24 hours or less [Hirsch and Gardner (298)]. Similar differential survivals were obtained by other techniques in the same circumstances [Stefanini & Chatterjea (299)]. It was shown that complement is used and fixed in purpura from allyl-isopropyl-

acetyl-carbamide (Sedormid) in producing platelet lysis [Ackroyd (300)], furthering the antigen-antibody theory in this process.

Congenital or neonatal thrombocytopenic purpura has been reported in 51 instances, the causes may be classified as follows: (a) children of mothers with idiopathic thrombocytopenic purpura, (b) primary infantile idiopathic thrombocytopenic purpura, (c) hypoplasia of the marrow [Robson & Walker (301)] An infant with a huge hemangioma developed thrombocytopenic purpura, recovering after splenectomy. There are two other cases citable [Bogin & Thurmond (302)] "Thrombotic" thrombocytopenia is reported as a collagen disease which may last three years in contrast to its customary acerbity [Meacham *et al.* (303)].

IRREGULAR PROTEIN PATTERNS IN HEMATOLOGIC DISEASE

The irregular serum protein distribution patterns which extend across the entire spectrum of disease frequently accompany the hematologic disorders

Disseminated lupus, a so-called collagen disease, with its symptomatic hyperglobulinemia, leucopenia, anemia, hemolysis, thrombocytopenia and "L. E. cell" are fully discussed elsewhere.

Cryoglobulins, identified with "cold purpura" (Waldenstrom, 1937) were beautifully studied after isolation [Barr *et al.* (304), Luckey *et al* (305)] as to chemical and biologic significances

Two further types of purpura have been described with cryptogenic hyperglobulinemia by Waldenstrom (306). Currently reported instances of Waldenstrom's third type were reported as a patient with "plasmacytoma of the alpha-gamma type" and nephrosis [Esser (307)], as a patient with "lymphatic reticulosis" and excess beta globulin [Tischendorf & Hartmann (308)], and another with excess gamma globulin, marrow plasmacytosis, and reticulum cell hyperplasia [Horster (309)]. The cause of this general class is not generally assignable [Waldenstrom (306)]

Diffuse plasmacytosis and hyperglobulinemia was expressed as a manifest of sulfonamide sensitivity in two cases [Robertson (310)] Relative plasmacytosis up to 3 4 per cent was seen in children with rheumatic fever (normal 0 38 per cent) [Good & Campbell (311)] Studies on 33 patients with high globulin levels of varied origin indicated elevated marrow plasmacytes in 6 of 33 and elevated eosinophils in one of the three cases [Berlin *et al* (312)]. In 1300 patients undergoing protein studies unexplained high globulins were discovered in 12; 11 of the 12 were females with a prolonged illness characterized by fever, arthralgia, and arthritis, and marked liver but not marrow plasmacytosis [Kunkel *et al* (313)] This illness was not identified In a male showing constant hyperglobulinemia and initial peripheral lymphocytosis with marrow lymph-plasmocytosis diminishing over ten years, there were constant peripheral neuropathy, disturbed cerebrospinal fluid proteins and Bence/Jones proteosuria No diagnosis was secured at autopsy [Bichel *et al* (314)]

ADRENOCORTICOTROPHIN-CORTISONE EFFECTS IN HEMATOLOGY

It is general belief that the major hematologic effects of the pituitary adrenocorticotrophin (ACTH) are mediated by adrenal release of the 11-oxy-steroid, compound F, the action of which is closely mimicked by its dehydro analogue compound E or cortisone. Distribution channels have produced greater data on the hematologic effects of ACTH than of cortisone, and there is yet little published material on the natural analogue F. Preliminary general statements of the therapeutic roles of hormones in hematology have been offered [Wintrobe (315); Thorn *et al.* (316)].

Hemolytic anemias.—Successful reduction of anemia due to acquired hemolysis in the idiopathic and in the majority of known secondary or symptomatic causes has resulted from ACTH therapy [Dameshek *et al.* (317); Wintrobe (315); Thorn *et al.* (316); Unger (318); Carpenter (31); Dubois (75)] or from cortisone [Ley & Gardner (319)] The titrable circulating antibodies may be reduced [Dameshek *et al.* (317)] or may remain fixed despite improvement [Ley & Gardner (319)] Relapse on cessation of therapy is the rule, unless there is modification of the symptomatic cause as in infectious cases or in leukosis. The anemia of congenital microspherocytosis was not improved in two instances [Davidson *et al.* (320)].

Purpura.—A high proportion of idiopathic thrombocytopenic purpuras responded to ACTH [six of six cases, Bethell *et al.* (321), nine of nine cases, Carpenter (31); three of four cases, Faloon *et al.* (322)] or cortisone [Bethell *et al.* (321)]. Platelet counts commonly rose after seven to ten days, though hemorrhage often ceased earlier. In a case resistant to splenectomy the platelet level rose twice when specifically stimulated by ACTH [Evans & Liu (323)] This earlier effect may have been due to a non-specific rise in capillary resistance, as regularly induced in six arthritics by 25 mg ACTH [Robson & Duthie (324)] four hours after injection. In a child with anaphylactoid purpura and nephritis ACTH arrested the hemorrhage but not the nephritis [Stefanini *et al.* (325)] Conversely, two instances of hemorrhagic syndromes apparently due to renal loss of ascorbic acid have followed prolonged therapy (115 days and 85 days) of ACTH, terminable by ascorbic acid saturation [Rosenthal (326)].

Blood coagulation.—Post ACTH (or cortisone) studies of the Lee-White and Waugh-Ruddick heparin-delayed coagulation time led to the postulate of hypercoagulability of the blood as explanation of 11 instances of thrombophlebitis in 175 patients [Cosgriff *et al.* (327)]. However, in another series only 5 patients in 200 were afflicted, 4 immediately after cessation of therapy [Hume & Moore (328)].

Leukotic disease.—Since the first declaration of hormonal effectiveness in the leukotic tumors [Pearson *et al.* (329)], a large volume of experience is available, though much of it is contributed in partially collated communications General experience may be thus summarized. (a) acute pediatric leukemia is most sensitive with best remissions, followed in order by (b) acute adult leukemia, (c) chronic lymphatic leukemia, (d) lymphosarcoma.

The effect on monocytic granulocytic leukemia and on Hodgkins disease is unsatisfactory and on occasion definitely harmful Readers are referred to the publications detailing the evidence [Pearson *et al.* (330); Farber *et al.* (331, 332); Eliel (333); Rosenthal *et al.* (334); Snelling *et al.* (335), Videback (336), Schulman *et al.* (337)]. Analysis of the length of induced remission by hormonal means in children [Pierce (338)] indicated that remissions were considerably shorter than spontaneous remissions [Diamond & Luhby (188)]. It has been stated that (for children) the remissions induced hormonally are less satisfactory than those induced by the folic acid blocking agents [Farber *et al.* (332)]. There is no cross reference of the remissions induced hormonally and by antagonists and either may succeed when resistance has developed to the other mode [Schulman *et al.* (337), Carpenter (31)] Contrary to the average mode of reaction, leukoses may show unexpected good results (perhaps within the natural unpredictability). Thus a monocytic leukemia has shown a marked remission after treatment by ACTH [Kinsell *et al.* (339)]. Despite reported negative effects on anemia, proteinemia, and marrow plasmatocytosis in multiple myeloma [Pearson *et al.* (340), Engle & Barr (341)], individual good responses [Eliel (342); Engel (343)], particulary in regard to pain in four of eight patients [Bethell (344)] are reported.

Miscellaneous effects—In two cases of sarcoid there was marked clinical amelioration on cortisone [Sones *et al.* (345)]. In miscellaneous forms of refractory anemia including hypoplastic and myelofibrotic good though not complete improvement has been repeatedly reported [Gardner in (346); Hill & Hunter (347) with contributory discussion by Klein, Loeb, Schulman & Bethell]. However, disappointing results are also obverted (347), which is uniformly this reviewer's experience.

A reticulocytosis (6 2 per cent, ACTH; 7.5 per cent, cortisone) occurred regularly in hormone treated rheumatoid arthritis [Finch *et al* (348), Havermark & Norderson (349)]. The refractory anemia of nephritis has improved [Carpenter (31)] Corticotropin induced marked hematologic and clinical improvement in a child with Cooley's anemia [Whitelow (350)], but the reticulocytosis and normoblastosis uniformly produced in this disease did not affect the high serum iron or low mean corpuscular hemoglobin [Schulman (351)] The production of crisis by ACTH is referred to in the paragraph on sicklemia. Successful use of ACTH in agranulocytosis is claimed [Caldwell *et al* (352); McMillin (353)], but a proper caution is essential in interpreting such sparse data.

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DISEASES OF THE RESPIRATORY SYSTEM[1]

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For this review only a few topics were chosen from the large field of respiratory diseases The selections may reflect the reviewers' personal interests However, an attempt was made to discuss at some length two common diseases, bronchogenic carcinoma and tuberculosis, and to call attention briefly to several less common entities for which there should be a growing awareness.

Bronchogenic Carcinoma

The increased incidence of bronchogenic carcinoma continues to be discussed actively in the literature. Most authors now conclude that the increase is real rather than apparent In an analysis of necropsy data from Los Angeles, Steiner *et al.* (1) note that carcinoma of the lung was present in 0 6 per cent of all autopsies and it made up 4 3 per cent of all tumors, in the years 1923 to 1927, while in the period 1943 to 1946, its incidence was 2 3 per cent of autopsies and 11 3 per cent of tumors. In their opinion, the increased incidence could not be explained by improved recognition of the entity by pathologists or by a change in the male:female ratio in the community, or by the greater age of the population as a whole. Saxton (2), in a study of autopsy material from St Louis, states that in the period 1935 to 1940, the incidence of lung cancer in all autopsies was 1.5 per cent; while in the period 1945 to 1950, the incidence was 2.5 per cent. This is an increase of 66 per cent in lung cancer, in contrast to an increase of 23 per cent in all other cancers Zissler (3), analyzing a European series, also concludes that the increased incidence is real rather than apparent. In another European study [Koch (4)], the incidence of carcinoma of the lung among all carcinomas seen at autopsy rose from 3 6 per cent in the period 1920 to 1923 to 26 2 per cent from 1945 to 1948 The opposing point of view is presented by Rigdon & Kirchoff (5) who, from an analysis of autopsy material in Galveston, Texas, conclude that the increase in bronchogenic carcinoma is due to an aging population.

Graham (6) points out that cancer of the lung is overwhelmingly a disease of males. He believes that excessive cigarette smoking is an important etiologic factor, though, of course, not the only one Doll & Hill (7) have also come to the conclusion that cigarette smoking of long duration is closely re-

[1] The survey of literature pertaining to this review was completed in October, 1951.

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cidence of false negatives was 31 per cent while the incidence of false positives was 4 per cent. It is interesting that in their series two-thirds of the resectable cases had a positive cytologic examination. In a series of 588 patients with miscellaneous chest diseases reported by Woolner & McDonald (14), there were 93 cases of bronchogenic carcinoma The incidence of a positive biopsy in these patients was 41 per cent, while the incidence of the positive cytologic examination was 70 per cent. There were no false positive cytologic examinations. In 61 cases of adenocarcinoma reported by Patton *et al.* (15) from the Mayo Clinic, positive cytologic examinations were obtained in 63 per cent; while in 116 cases of squamous-cell carcinoma from the same clinic reported by Carlisle *et al.* (12), the incidence of positive cytologic examinations was 72.4 per cent That the percentage of positive cytologic examinations is related to the number of specimens examined is pointed out by Farber and co-workers (16). In a study of 2,000 patients, the incidence of positive cytologic examinations rose from 55 per cent, when one specimen was examined, to 90 per cent, when five specimens were examined. There appears to be no doubt that the cytologic examination is a valuable aid in the diagnosis of bronchogenic carcinoma, especially in those cases where bronchoscopy is negative or equivocal However, the diagnostic value of a positive cytologic examination is relative to roentgenographic and clinical indications for exploratory thoracotomy. When diagnostic exploratory thoracotomy is carried out without delay in cases where symptoms and x-ray shadows are suggestive of bronchogenic carcinoma, the positive cytologic examination may serve only to shorten the diagnostic period prior to operation. Whether this shortening of the diagnostic period, in terms of several weeks, is of great moment in the end results is questionable. In situations where, for various reasons, exploratory thoracotomy cannot be freely undertaken, for example, in the case of the poor-risk patient, the positive cytologic examination may be of very great diagnostic aid.

The results of surgery in bronchogenic carcinoma were reported from several clinics. Churchill and co-workers (17) report the experience of the Massachusetts General Hospital in the period 1930 to 1950, primarily from the point of view of lobectomy versus pneumonectomy in the treatment of bronchogenic carcinoma. Pneumonectomies were performed on 87 patients prior to 1928 and of these, 19, or 22 per cent, have survived Of those patients who were treated by lobectomy 26 per cent survived. In this series there is the inherent difficulty of comparing lobectomy with pneumonectomy since the indications for the two operations were different. One may, however, conclude that in selected cases lobectomy may be as satisfactory as pneumonectomy in the treatment of bronchogenic carcinoma. Moore (10) records the experience of Presbyterian Hospital, New York City, in 370 patients with bronchogenic carcinoma Forty-two per cent were explored, and slightly more than half of these were resected Seventy-two per cent of the resections were pneumonectomies, 28 per cent, lobectomies. Thirty-one patients were operated upon prior to 1946; of these 13 per cent have survived five years

lated etiologically to bronchogenic carcinoma. Upon interviewing patients with bronchogenic carcinoma they found that 0.3 per cent of men and 31.7 per cent of women were non-smokers. The corresponding figures in non-cancer controls were 4.2 per cent and 52.3 per cent. Graham (6) states that the marked increase in bronchogenic carcinoma has been in the epidermoid rather than in the adenocarcinoma or round and oat cell types. He suggests that the squamous cell variety represents a metaplasia occurring under the influence of a variety of carcinogenic agents, such as cigarette smoking; while the other varieties arise from latent bronchial tissue. He asserts that when a bronchogenic carcinoma occurs in a patient who has never smoked, it is likely to be an adenocarcinoma or one of its variants. Dungal (8) states that bronchogenic carcinoma is a rare disease in Iceland, a fact which he attributes to the relative recency of cigarette smoking in that country. However, the consumption of cigarettes is mounting and, estimating that 20 to 25 years of smoking is required to cause bronchogenic carcinoma (if smoking is one of the causes), he anticipates that an increased incidence will be apparent in the years 1960 to 1965. The situation of Iceland in this respect may furnish a unique type of control in the study of bronchogenic carcinoma.

In spite of an increased awareness of the high incidence of bronchogenic carcinoma, the number of unresectable cases reported continues to be appallingly high. Paulson & Shaw (9), reviewing their experience of the past 3½ years, state that 50 per cent of 263 patients with bronchogenic carcinoma were considered inoperable when first seen. About one-fourth of the patients had clinical evidence of metastases indicating inoperability. Of the 182 patients who were explored, slightly more than half were considered resectable. Moreover, in half of those resected the operation was considered palliative. In Moore's (10) series, 42 per cent of 370 patients were considered operable, and hardly more than half (56 per cent) of those explored were thought suitable for resection. In the Boston Survey (11) also, about 50 per cent of 43 cases of primary cancer of the lung were inoperable, a rather disconcerting figure considering that this was a survey of apparently healthy individuals. In Graham's (6) series, approximately 40 per cent of cases were explored, and pneumonectomy was carried out in 25 per cent. In 175 cases of bronchogenic carcinoma from the Mayo Clinic reported by Carlisle et al. (12) both the operability and resectability rates were 71 per cent. The reasons for the differences in operability and resectability rates in the literature are difficult to assess since the criteria for each are not always clearly set forth.

Judging from the number of reports in the literature, there appears to be a [illegible] of bronchogenic carcinoma. As [illegible] rom [illegible] r of specimens examined, and the type of clinical material analyzed. Jackson et al. (13) in a study of the cytology of expectorates and bronchial secretions of 270 patients with a variety of pulmonary diseases, report an incidence of 61 per cent positive results in 100 cases of bronchogenic carcinoma. The in-

discovered by routine x-ray, and 12 of the 52, or 22 per cent, were malignant. Harrington (22) emphasizes the need for exploratory thoracotomy in order to establish or rule out the malignancy in such lesions Husfeldt & Carlsen (23) report an interesting group of 33 patients with round, sharply demarcated solid lesions Four of these were shown to be primary bronchogenic carcinoma, while three were malignancies of other types. Two were tuberculomas Husfeldt also emphasizes the role of diagnostic thoracotomy in differentiating carcinoma from other entities which cast round, well-demarcated shadows on the x-ray. These studies demonstrate that the x-ray appearance of bronchogenic carcinoma, at an early stage may resemble tuberculosis, benign pulmonary tumors, cysts of various origins, developmental anomalies, and a host of miscellaneous entities When diagnostic thoracotomies are carried out for small lesions discovered upon routine x-ray films, many non-cancerous lesions will be found. However, as Liavaag (24) points out, while the large number of chronic pulmonary diseases resembling bronchogenic carcinoma may not be life-threatening, many are best treated by resection The long term results of excision of small bronchogenic carcinomas should be eagerly awaited. Overholt (25) emphasizes the value of tuberculosis finding surveys for detecting early pulmonary cancer. He feels that bronchogenic carcinoma has a silent phase which should be more amenable to cure if surgery is promptly applied In the Overholt Clinic, during 1950, 61 per cent of 54 cases of primary cancer of the lung did not have an absolute diagnosis preoperatively

The poor results of resection in the treatment of bronchogenic carcinoma and the great number of inoperable cases have stimulated more interest recently in palliation by deep x-ray therapy and chemotherapy. Occasionally, beneficial results are observed with chemotherapy [Kent & Reh (26), Ayers (27)] However, it is the consensus that this form of treatment generally offers very little The palliative results of x-ray therapy however, are more encouraging Brooks *et al.* (28), reporting the work of the Joint Consultation Clinic for Neoplastic Disease of the Brompton Hospital and the Royal Cancer Hospital, make a distinction between palliative and radical x-ray therapy In their experience the value of radical x-ray therapy has been marked Relief of hemoptysis is almost constant. Relief of superior vena caval obstruction is one of the most useful effects of irradiation. Pain from bone metastases is frequently relieved. In their opinion, the primary tumor can, in rare instances, be made to disappear by irradiation Of 176 patients in this series treated with palliative irradiation, 171 are dead after an average survival of 5 6 months after therapy, while patients receiving radical x-ray therapy survived an average of 10 months They believe that irradiation is seldom worth while trying in patients in poor condition In their experience no real benefit has been seen with chemotherapy in 54 cases treated. Results of irradiation therapy from the Liverpool Radium Institute (18) show an average survival rate of 7 6 months for 916 untreated cases, and 14 7 months for 190 cases radically treated by irradiation It may be that the value of

or more. When pneumonectomy patients were classified according to lymph node involvement, the survival rates were in close agreement. Graham (6) reports a five year survival rate of 28 per cent for those patients who underwent pneumonectomy. These cases were approximately five per cent of the total number of patients originally in that series. In a study from the Cancer Follow-up Department of the Birmingham United Hospitals (18) the five year survival rate for 313 pneumonectomies was 13.7 per cent. The five year survival rate for 121 cases of squamous-cell carcinoma resected at the Mayo Clinic is 51.9 per cent, as reported by Carlisle *et al.* (12). According to these authors "given 100 patients with proved squamous cell bronchogenic carcinoma, it can be said on the basis of this study that 71 will be operable, 50 will have resectable lesions, 47 will survive, and 24 will be alive in 5 years" The survival rate following pneumonectomy or lobectomy for adenocarcinoma in the same group was considerably less favorable, only one-third of the cases being alive at the end of two years (15).

The removal of solitary pulmonary metastases from extra pulmonary cancers deserves brief comment. Rudström (19) presents a review of the earlier published cases and adds two of his own. It is his opinion that the removal of pulmonary metastases is justified if the primary tumor has been radically removed. In his experience the survival rate is best for sarcomas Alexander & Haight (20) report 14 cases with a follow-up of 1 5 to 10 years Good results have been achieved in 5 out of the 14 cases Complete removal of the primary tumor and unilateral metastases without pleural involvement comprise their indications.

The poor results of treatment of bronchogenic carcinoma have resulted in an interest in earlier diagnosis, and special attention has been directed toward the lesions variously designated, "solitary" or "circumscribed" pulmonary lesions. This type of small, well-demarcated lesion, almost invariably discovered during routine chest surveys, is the subject of several interesting reports during the past year. Abeles & Ehrlich (21) report 44 cases with such circumscribed intrathoracic lesions Exploratory thoracotomy was advised in 31 cases in which malignancy could not be ruled out, and malignant lesions were found in seven In five other patients who refused operations, the presumptive diagnosis of malignancy was made by the subsequent clinical course. The criteria of benign disease in the 13 patients for whom operation was not advised are worth enumerating. In eight patients malignancy was considered unlikely because of calcification within the lesions; in three patients, because previous x-rays showed stability of the lesions; and in the remaining two, because of a positive coccidioidin test together with a history of residence in the southwestern part of the country The presence of calcification within these circumscribed lesions is usually taken as evidence of a tuberculous etiology. This is true in the great majority of cases However, it is worth while pointing out that malignant lesions do occasionally arise in an area of previous calcification. Another series of 291 circumscribed intrathoracic lesions is presented by Harrington (22) Fifty-two of these had been

noted albuminuria, azotemia, hypokalemia, hypocalcemia, hypochloremia, impairment of vestibular function, and deafness They stated however, that these toxic effects could be controlled and, in their opinion, did not preclude the use of this agent

The therapeutic efficacy of viomycin could hardly be evaluated in this small series. Later in the year, at the 10th Streptomycin Conference, Muschenheim (39) summarized the results obtained by several study units investigating viomycin This report, which included 49 patients, confirmed in general the earlier one of Werner *et al* (38) relative to the toxicity of this agent All patients had albuminuria and cylindruria, and decreased renal function was frequent. These renal abnormalities were reversible when the drug was discontinued. Vestibular damage was observed in one-fifth of the cases. Electrolyte disturbances were common though not severe Improvement by x-ray was seen in approximately half of the cases, and was marked in only four instances It should be noted, however, that many cases had had streptomycin previously and in general presented difficult therapeutic problems Muschenheim (39) concluded that viomycin has therapeutic potentialities which are less than those of streptomycin, and that its toxicity is greater than, though similar to, that of streptomycin. He believed that the number of cases was too small for an accurate estimate of the drug's value, and that further clinical trials were warranted. Smaller dosages of viomycin in an effort to reduce toxicity, and its combination with PAS in order to increase therapeutic efficacy, are now being investigated At this writing the toxicity of viomycin in dosage of 50 mg per kg. daily (the dosage used in the earlier clinical trials) is such as to preclude its use except under the most careful laboratory control.

Terramycin, a broad-spectrum antibiotic derived from *Streptomyces rimosus*, has moderate bacteriostatic activity against the tubercle bacillus According to Hobby *et al.* (40), 4 to 16 μg per ml are sufficient to inhibit most strains of tubercle bacilli, including those resistant to streptomycin. In experimental tuberculous infections Steenken & Wolinsky (41) demonstrated definite activity in guinea pigs infected with both streptomycin-sensitive and streptomycin-resistant bacilli. In a seminar on terramycin in the treatment of pulmonary tuberculosis at the 10th Conference on the Chemotherapy of Tuberculosis (42), several study units reported preliminary clinical trials with this agent Therapeutic results were not impressive However, one study group (Fitzsimmons General Hospital, Denver, Colorado) reported encouraging results and was moderately sanguine about its therapeutic potentialities At this hospital most of the patients were able to tolerate seven grams of terramycin per day, the dosage set forth in the protocol of the study. It is possible that this unusual tolerance may explain the apparently superior therapeutic results in that group. Other study units had considerable difficulty in having patients tolerate that amount, and irregularities and reductions in dosage were frequent. It was the consensus of the 10th Conference that terramycin has tuberculostatic properties of a low order in

irradiation of bronchogenic carcinoma should not be measured so much by survival rates as by the relief of symptomatology. The favorable effects of x-ray therapy in the relief of symptoms and prolongation of life is also discussed by Willbold (29). It is anticipated that developments in the technique of irradiation therapy will contribute further to the palliation of inoperable bronchogenic carcinoma.

TUBERCULOSIS

While streptomycin has been of great value in the treatment of tuberculosis, the bacterial resistance which so frequently follows has been a serious disadvantage. The administration of *p*-aminosalicylic acid (PAS) in combination with streptomycin has diminished the incidence of streptomycin-resistance to an appreciable degree, yet tubercle bacilli do become resistant to both agents. Retreatment with streptomycin is then usually of no avail The introduction of new drugs is therefore a matter of great interest in the field of tuberculosis therapy. New agents may be used to treat patients whose organisms are already resistant to streptomycin, and the fact that other drugs are available also liberalizes the indications for streptomycin therapy in new cases

Viomycin, one of the more recent tuberculostatic antibiotics, was announced at the 9th Streptomycin Conference in April, 1950, by Patelski (30). Publications by workers from the laboratories of two commercial producers of antibiotics subsequently appeared [Finlay *et al.* (31), Ehrlich *et al.* (32)]. *This antibiotic derived from Streptomyces puniceus is a strongly* basic sub- [illegible] and streptomycin-resistant [illegible] g per ml. It is, moreover, [illegible] *inst other microörganisms* only in relatively high concentrations. Bacterial resistance to viomycin occurs both *in vitro* and *in vivo*, much as in the case of streptomycin, though possibly at a slower rate.

The effectiveness of viomycin in experimental tuberculosis has been demonstrated by Hobby *et al* (33) and by Youmans & Youmans (34). Steenken & Wolinsky (35) and Karlson & Gainer (36) showed that viomycin was effective in animals infected with streptomycin-resistant tubercle bacilli. As assessed in the experimental animal, however, this new agent is only approximately one-fourth as effective as streptomycin (35), a point of the greatest importance in its application to therapy in man

The toxicity of viomycin in experimental animals according to P'an *et al.* (37) is low They reported that dogs tolerated to 50 to 100 mg. of viomycin per kg. for more than 150 days without significant toxicity. Cats receiving the drug *in that dosage, however, showed disturbances of posture* and gait. Werner and co-workers (38) reported the results of viomycin therapy in 10 tuberculous patients receiving 30 to 75 mg per kg. for 114 to 182 days. In contrast to the *relative lack of toxicity in experimental animals,* viomycin was found to have severe toxicity in man. These investigators

usually protracted, it affords an opportunity to observe the characteristically late toxicity of dihydrostreptomycin. Short courses of 56 to 90 days appear to cause no immediate auditory damage [Lincoln *et al.* (53)]. Studies with the prolonged administration of dihydrostreptomycin sulphate are now in progress The results will be eagerly awaited. In the meantime, because of the growing tendency to employ longer courses of chemotherapy in the treatment of pulmonary tuberculosis, the potential auditory toxicity of dihydrostreptomycin should be borne in mind.

During the past year investigators both in this country and abroad have attempted to assess the efficacy and toxicity of the thiosemicarbazones in the treatment of tuberculosis A rather clear picture of the toxicity of these compounds has now emerged. Those toxic manifestations, chiefly hepatic, gastro-intestinal, and hematologic, first reported have been confirmed by later studies The toxicity of TB-1[2] as observed in 309 patients treated in the Study Units of the Veterans Administration, Army, and Navy Hospitals was summarized by Bunn (54) at the 9th Streptomycin Conference. Therapy was terminated in 75 patients because of toxicity. In 31 of the 75 there was evidence of liver damage, 20 had a variety of hematologic abnormalities, while in 38 nausea, vomiting, and anorexia were severe enough to prompt withdrawal of the drug. Ten deaths occurred in this series. In two of these the toxicity of TB-1, severe hemolytic anemia in one and granulopenia in the other, may have been contributing factors. At the 10th Streptomycin Conference (55) the collected data of the Study Units on approximately 200 cases receiving TB-1 revealed liver damage in 22 per cent, blood dyscrasias in 11 per cent, and nausea and vomiting in 26 per cent. There is now general agreement that the great majority of these abnormalities are reversible as soon as the drug is withdrawn. It is evident that the thiosemicarbazones may be used in dosages of 100 to 200 mg per day with comparative safety provided a moderate amount of laboratory supervision is possible. Larger doses, so well studied by Simmons *et al* (56) are considerably more toxic.

The therapeutic efficacy of the thiosemicarbazones has been much more difficult to evaluate In experimental tuberculous infection there is no doubt whatsoever that these compounds are effective Steenken & Wolinsky (57) have demonstrated that their therapeutic efficacy in guinea pigs is approximately one half that of streptomycin, and considerably greater than that of PAS This in confirmed by Spain *et al* (58). These experimental results, however, have been achieved by dosages which are comparable to 3.0 gm. per day for an average patient, a dosage which is absolutely precluded by the toxicity of these compounds.

It is impossible here to review in detail the reports of clinical trials with the thiosemicarbazones that have appeared during the past year The majority of authors agree that these agents have a definite though modest antituberculous activity in human tuberculous infection [Belgorod *et al.* (59), Davis *et al* (60), Livingstone & Street (61), Skavlem *et al.* (62)]. Probably

[2] *p*-Formylacetanilide thiosemicarbazone

human tuberculosis, and that its efficacy awaits exact quantification. Further clinical trials with terramycin on a small scale seemed warranted. It is probable that the combination of terramycin and streptomycin for the purpose of combating streptomycin-resistance (in much the same way as PAS is used) offers more promise than the use of terramycin alone.

Neomycin, an antibiotic substance derived from *Streptomyces fradiae* announced by Waksman & Lechevalier (43) in 1949, is effective against both streptomycin-sensitive and streptomycin-resistant tubercle bacilli. It inhibits tubercle bacilli in concentrations of 0.3 to 20.6 units per ml. and has a marked beneficial effect on experimental tuberculosis [Steenken *et al.* (44), Karlson *et al* (45)]. However, neomycin has been used in treating tuberculosis to only a very limited degree. Its toxicity, chiefly renal damage and hearing loss, is such that it is hardly adaptable for the treatment of a chronic infection. Kadison *et al* (46) have used neomycin in a few tuberculous patients and have noted hematuria, albuminuria, and complete deafness The results, moreover, in advanced tuberculosis were not encouraging. Carr *et al* (47) report clinical trials with neomycin in five patients whose tubercle bacilli were resistant to streptomycin The duration of therapy was for 29 to 52 days. Three had symptomatic improvement, in only one was there roentgenographic evidence of improvement. Transient renal damage occurred in all. Progressive deafness occurred in four.

When dihydrostreptomycin was first employed its auditory toxicity was debated in terms of large doses, viz, 2 to 3 gm. per day Now, however, there is increasing evidence that dihydrostreptomycin in a dosage of but 1 gm per day causes far greater auditory damage than streptomycin in comparable dosage provided administration is continued beyond four months D'Esopo & Raleigh (48) noted progressive auditory damage necessitating discontinuation of the drug in five patients treated with 1 gm of dihydrostreptomycin hydrochloride and 9 gm of PAS daily for six or more months. Control cases receiving 1.0 gm of streptomycin and 9 gm of PAS daily occasionally showed slight hearing loss in the highest frequency range, and in no case was chemotherapy discontinued because of hearing loss Subsequently, Howlett (49) reported moderate to complete hearing loss in 19 patients treated for six months with 1 0 gm. of dihydrostreptomycin and PAS daily. These data were elaborated upon later by O'Connor, Christie, & Howlett (50) The experience of these investigators was concerned with the hydrochloride salt of dihydrostreptomycin. Because this preparation is much more irritating locally than the sulphate, it is possible, though quite unlikely, that the deafness caused by this salt is due to impurities rather than to the dihydrostreptomycin base itself Minkenhof (51) states unequivocally that dihydrostreptomycin causes deafness in a high percentage of patients treated for tuberculous meningitis. Beyer *et al.* (52) report two series of children, one treated with dihydrostreptomycin, the other with streptomycin. Deafness occurred with much greater frequency in the dihydrostreptomycin-treated children Deafness in meningitis may of course be due to the disease per se, but because the treatment of meningitis is

usually protracted, it affords an opportunity to observe the characteristically late toxicity of dihydrostreptomycin. Short courses of 56 to 90 days appear to cause no immediate auditory damage [Lincoln *et al.* (53)]. Studies with the prolonged administration of dihydrostreptomycin sulphate are now in progress. The results will be eagerly awaited. In the meantime, because of the growing tendency to employ longer courses of chemotherapy in the treatment of pulmonary tuberculosis, the potential auditory toxicity of dihydrostreptomycin should be borne in mind.

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human tuberculosis, and that its efficacy awaits exact quantification Further clinical trials with terramycin on a small scale seemed warranted It is probable that the combination of terramycin and streptomycin for the purpose of combating streptomycin-resistance (in much the same way as PAS is used) offers more promise than the use of terramycin alone.

Neomycin, an antibiotic substance derived from *Streptomyces fradiae* announced by Waksman & Lechevalier (43) in 1949, is effective against both streptomycin-sensitive and streptomycin-resistant tubercle bacilli It inhibits tubercle bacilli in concentrations of 0 3 to 20 6 units per ml and has a marked beneficial effect on experimental tuberculosis [Steenken *et al.* (44), Karlson *et al.* (45)]. However, neomycin has been used in treating tuberculosis to only a very limited degree. Its toxicity, chiefly renal damage and hearing loss, is such that it is hardly adaptable for the treatment of a chronic infection. Kadison *et al.* (46) have used neomycin in a few tuberculous patients and have noted hematuria, albuminuria, and complete deafness The results, moreover, in advanced tuberculosis were not encouraging Carr *et al.* (47) report clinical trials with neomycin in five patients whose tubercle bacilli were resistant to streptomycin. The duration of therapy was for 29 to 52 days. Three had symptomatic improvement; in only one was there roentgenographic evidence of improvement Transient renal damage occurred in all. Progressive deafness occurred in four.

When dihydrostreptomycin was first employed its auditory toxicity was debated in terms of large doses, *viz*, 2 to 3 gm. per day Now, however, there is increasing evidence that dihydrostreptomycin in a dosage of but 1 gm. per day causes far greater auditory damage than streptomycin in comparable dosage provided administration is continued beyond four months. D'Esopo & Raleigh (48) noted progressive auditory damage necessitating discontinuation of the drug in five patients treated with 1 gm. of dihydrostreptomycin hydrochloride and 9 gm of PAS daily for six or more months Control cases receiving 1.0 gm of streptomycin and 9 gm of PAS daily occasionally showed slight hearing loss in the highest frequency range, and in no case was chemotherapy discontinued because of hearing loss Subsequently, Howlett (49) reported moderate to complete hearing loss in 19 patients treated for six months with 1 0 gm. of dihydrostreptomycin and PAS daily These data were elaborated upon later by O'Connor, Christie, & Howlett (50) The experience of these investigators was concerned with the hydrochloride salt of dihydrostreptomycin. Because this preparation is much more irritating locally than the sulphate, it is possible, though quite unlikely, that the deafness caused by this salt is due to impurities rather than to the dihydrostreptomycin base itself Minkenhof (51) states unequivocally that dihydrostreptomycin causes deafness in a high percentage of patients treated for tuberculous meningitis Beyer *et al* (52) report two series of children, one treated with dihydrostreptomycin, the other with streptomycin Deafness occurred with much greater frequency in the dihydrostreptomycin-treated children. Deafness in meningitis may of course be due to the disease per se, but because the treatment of meningitis is

usually protracted, it affords an opportunity to observe the characteristically late toxicity of dihydrostreptomycin. Short courses of 56 to 90 days appear to cause no immediate auditory damage [Lincoln *et al.* (53)] Studies with the prolonged administration of dihydrostreptomycin sulphate are now in progress The results will be eagerly awaited. In the meantime, because of the growing tendency to employ longer courses of chemotherapy in the treatment of pulmonary tuberculosis, the potential auditory toxicity of dihydrostreptomycin should be borne in mind

During the past year investigators both in this country and abroad have attempted to assess the efficacy and toxicity of the thiosemicarbazones in the treatment of tuberculosis. A rather clear picture of the toxicity of these compounds has now emerged Those toxic manifestations, chiefly hepatic, gastro intestinal, and hematologic, first reported have been confirmed by later studies. The toxicity of TB-1[2] as observed in 309 patients treated in the Study Units of the Veterans Administration, Army, and Navy Hospitals was summarized by Bunn (54) at the 9th Streptomycin Conference Therapy was terminated in 75 patients because of toxicity. In 31 of the 75 there was evidence of liver damage, 20 had a variety of hematologic abnormalities, while in 38 nausea, vomiting, and anorexia were severe enough to prompt withdrawal of the drug Ten deaths occurred in this series In two of these the toxicity of TB-1, severe hemolytic anemia in one and granulopenia in the other, may have been contributing factors. At the 10th Streptomycin Conference (55) the collected data of the Study Units on approximately 200 cases receiving TB-1 revealed liver damage in 22 per cent, blood dyscrasias in 11 per cent, and nausea and vomiting in 26 per cent. There is now general agreement that the great majority of these abnormalities are reversible as soon as the drug is withdrawn. It is evident that the thiosemicarbazones may be used in dosages of 100 to 200 mg per day with comparative safety provided a moderate amount of laboratory supervision is possible. Larger doses, so well studied by Simmons *et al* (56) are considerably more toxic

The therapeutic efficacy of the thiosemicarbazones has been much more difficult to evaluate In experimental tuberculous infection there is no doubt whatsoever that these compounds are effective. Steenken & Wolinsky (57) have demonstrated that their therapeutic efficacy in guinea pigs is approximately one half that of streptomycin, and considerably greater than that of PAS This in confirmed by Spain *et al.* (58). These experimental results, however, have been achieved by dosages which are comparable to 3 0 gm. per day for an average patient, a dosage which is absolutely precluded by the toxicity of these compounds.

It is impossible here to review in detail the reports of clinical trials with the thiosemicarbazones that have appeared during the past year. The majority of authors agree that these agents have a definite though modest antituberculous activity in human tuberculous infection [Belgorod *et al* (59), Davis *et al* (60), Livingstone & Street (61), Skavlem *et al* (62)]. Probably

[2] *p*-Formylacetanilide thiosemicarbazone.

somewhat less than the usually reported therapeutic efficacy was noted in the Pilot Trial organized by the Research Committee of the British Tuberculosis Association (63). One obtains the impression from the literature that the thiosemicarbazones in the dosages used (100 to 200 mg. per day) have an efficacy which is frequently discernible, but is, in general, too meager to appreciably alter the patient's therapeutic problem or to contribute much to his recovery At present there seems to be no place for the use of the thiosemicarbazones except in instances of streptomycin or PAS-resistance.

Acquired resistance to the thiosemicarbazones by the tubercle bacillus has been reported though its clinical significance has not been elucidated [Davis *et al* (60), Sandhaus *et al.* (64)] One would anticipate that this kind of correlation would be difficult in the case of an agent the efficacy of which is difficult to assess even when bacilli are completely sensitive to it.

The therapeutic efficacy of PAS (without streptomycin) was the subject of a great many reports during the past year. Its efficacy in man seems to exceed that of the thiosemicarbazones in spite of the superiority of the latter compounds *in vitro* and in experimental infections The explanation appears to lie in the fact that PAS can be used in very large doses (up to 24 gm. per day) and can be administered in long courses without important toxicity In general, PAS is an antituberculosis drug of only moderate therapeutic potentialities when used alone. In the Study Units of the Veterans Administration, Army, and Navy Hospitals (65), a group of 234 cases receiving 12.0 gm. of PAS daily for four months showed moderate or marked x-ray improvement in 18 per cent, and sputum conversion in 24 per cent. All patients were resistant to streptomycin. In a control series of streptomycin-resistant cases treated with both streptomycin and PAS the sputum conversion rate was similar, but 31 per cent of cases showed moderate or marked x-ray improvement While streptomycin-resistant patients form a special group and constitute a very severe test of a chemotherapeutic agent, nevertheless, certain basic evaluations can be made. A controlled study of PAS conducted by the Medical Research Council of England (66) clearly demonstrated that PAS is less effective than streptomycin and that the combination of streptomycin with PAS was more effective than streptomycin alone. While there seems to be no doubt that PAS is less active than streptomycin it is nevertheless the only drug now available which can be safely prescribed for the treatment of streptomycin-resistant patients. For these patients, retreatment with both streptomycin and PAS appears to be more efficacious than PAS alone (65)

The optimum dosage of PAS when employed without streptomycin is not known. Paraf *et al.* (67) assert that blood levels of 15 to 20 μg per ml are required for optimum effect. In order to obtain these levels 20 to 25 gm of PAS daily must be ingested. In a pilot study conducted by several Study Units in Veterans Administration Hospitals (68) patients had considerable difficulty in tolerating 24 gm. of PAS daily. In the great majority of cases it was necessary to reduce the dosage to 12 or 18 gm. daily In general, Euro-

pean investigators appear to have more success in having patients tolerate the larger dosages.

PAS has virtually no toxicity. However, severe hypersensitivity to PAS is frequently encountered. It is likely that the severe toxic symptoms occasionally attributed to PAS are really due to hypersensitivity. Sensitization appears between the second and fourth week and is characterized by fever, rash, headache, and arthralgia [Grandjean (69), Secousse *et al.* (70)]. If PAS is continued, jaundice, anemia, and anuria may supervene. An excellent, detailed report of a case of PAS hypersensitivity which includes many of the severe manifestations is given by Cuthbert (71). "Desensitization" by small, increasing doses of PAS is possible in the majority of cases

It has become the practice of many physicians to employ PAS without streptomycin so that the latter drug may be held in reserve for the treatment of serious complications. This plan, however, entails the risk of bacterial resistance to PAS Pugh *et al.* (72) state that resistance to PAS may occur in three to six months. This is the experience of most observers. On the other hand, Rist *et al* (73) assert that the tubercle bacillus may become resistant to PAS almost as rapidly as it does to streptomycin, while Paraf *et al.* (67), on the contrary, believe that not more than five to ten per cent of cases treated for several months exhibit resistant bacilli. Such variations in the incidence of PAS-resistant bacilli is explained by the technical difficulties of the methods used for testing bacterial resistance, and especially because in the *in vitro* test in liquid medium there is no sharp end-point between growth and inhibition. Another difficulty, of course, is the lack of agreement upon a definition of bacterial resistance to PAS Rist *et al.* (73), for example, suggest that growth in 2.5 μg per ml be the critical concentration separating resistant from sensitive cultures, since in their experience patients whose bacilli become that resistant fail to improve further. In general, the disadvantage of PAS-resistance has been minimized In the reviewers' opinion it is almost as important to preserve PAS-sensitivity as it is to preserve streptomycin-sensitivity Both of these desirable effects can be accomplished in a large majority of cases by the administration of streptomycin and PAS concomitantly Because of the risk of PAS-resistance it seems unwise to administer PAS alone except in the case of patients whose bacilli are highly resistant to streptomycin

The most important rôle of PAS in the treatment of tuberculosis is, in fact, its efficacy in inhibiting the emergence of streptomycin-resistant tubercle bacilli when it is used combined with streptomycin. A great mass of data has now been accumulated on this point. In a controlled study of several hundred cases, the Study Units of the Veterans Administration, Army, and Navy (74) reported an incidence of 25 per cent streptomycin-sensitivity in cases treated for four months with streptomycin alone, and an incidence of 53 per cent sensitivity in a group treated with both daily streptomycin and PAS for a corresponding period. A study conducted by the Medical Research Council of England (66) also demonstrated the effec-

tiveness of PAS in inhibiting streptomycin-resistance. A further extension of combined streptomycin-PAS is the development of the intermittent streptomycin-PAS regimen. This treatment, pioneered by the Fitzsimmons Group, appears to be more efficient than the daily administration of streptomycin, in so far as the inhibition of streptomycin-resistance is concerned. In their experience [Tempel *et al.* (75)], when patients received streptomycin every third day, and PAS daily for four months, none developed streptomycin-resistant bacilli. It should be pointed out that "resistant bacilli" in this and other studies is generally taken to mean bacilli which are inhibited by 10 or more µg. per ml. Bacterial resistance to concentrations of less than 10 µg. per ml., however, may occasionally be of clinical significance. The Fitzsimmons Group, as reported by Hughes and co-workers (76), also clearly demonstrated that PAS administered every third day together with streptomycin every third day is not as effective as daily PAS in preventing the emergence of streptomycin-resistant bacilli.

The intermittent streptomycin-PAS regimen is now regarded by most physicians as the regimen of choice. In May, 1951, a report of the Clinical Subcommittee of the Committee on Medical Research and Therapy (77) recommended

> that an intermittent regimen be used whenever streptomycin is to be given to a patient for tuberculosis, except for more serious forms such as miliary and meningeal tuberculosis in which daily treatment is advised.

This regimen is undoubtedly best adapted for general use. However, its efficacy relative to the daily streptomycin-PAS regimen still remains to be fully assessed in terms other than the preservation of streptomycin sensitivity. Nor has the intermittent regimen been adequately studied in prolonged courses.

The combined streptomycin-PAS regimen has made it possible to extend effective chemotherapy beyond four months. D'Esopo & Raleigh (48) describe their experience with prolonged combined streptomycin-PAS therapy in 50 patients. They conclude that the daily administration of both agents is feasible from the point of view of toxicity, that after the third month of combined therapy persistently negative cultures are obtained from the majority of patients even if large areas of cavitation persist, and that bacterial resistance to streptomycin is not significant as long as therapy is continued. In a further report, D'Esopo, Ryan & Medlar (78) present data confirming previous results. They state that the protracted clearing of shadows on x-ray during prolonged chemotherapy represents the resolution of areas of non-necrotic lobular pneumonia, while the shadows that remain behind are indicative of residual necrotic lesions, many of them filled-in cavities. These data were derived from a study of the pathology of lesions resected by wedge technique during chemotherapy of one year or more. These authors also present preliminary data on the bacteriology of necrotic lesions resected after prolonged chemotherapy. In several resected lesions tubercle bacilli, morphologically intact, were seen in great numbers. Yet

these could not be grown on culture medium. These findings, if confirmed, are of the greatest significance. The experience of Howlett (49) confirms in general that of D'Esopo *et al.* (48) in the value of prolonged combined chemotherapy in pulmonary tuberculosis

Pulmonary resection in tuberculosis has received great impetus since the introduction of chemotherapy. In general, chemotherapy in relation to resection is used in two fairly distinct ways: either as prophylaxis shortly before and briefly following resection, or for the preparation of patients for resection by prolonged administration. When chemotherapy is used as prophylaxis, the classical indications for resection usually prevail, namely, persistent cavitation after thoracoplasty, basal cavity, destroyed lung, bronchostenosis, and "tuberculous" bronchiectasis Pulmonary resection after prolonged chemotherapy, on the other hand, may be designed to remove by wedge or segmental resection small necrotic lesions which have not resolved during chemotherapy. There appears to be no question as to the value of chemotherapy as prophylaxis for pulmonary resection. In a series of lobectomies reported by the Study Units of the Veterans Administration, Army, and Navy (79), complications occurred in 13 per cent of 337 patients who received a first course of streptomycin prior to operation, and in 21 per cent of 321 patients who underwent lobectomy during retreatment with streptomycin In a group of 47 patients who were known to be resistant to streptomycin prior to operation, complications occurred in 43 per cent. Comparable results were reported in approximately 300 pneumonectomies, the corresponding figures being 22.6 per cent and 50 per cent respectively Similar results have been reported by Schaffner *et al* (80) In this series complications were recorded in 40 per cent of those patients who did not receive streptomycin prior to operation as compared to 10 per cent in the streptomycin-treated group.

When pulmonary resection has been performed for indications such as bronchostenosis, destroyed lung, etc, the prognosis has been favorable in those patients that did not succumb during or soon after the operation. Beatty and co-workers (81) report 93 consecutive pulmonary resections performed for the indications enumerated above 20 4 per cent of the patients are now known to be dead, but 92 per cent of the living patients have a negative sputum In Eerland's (82) group of 187 patients who have undergone pneumonectomy, lobectomy, or segmental resection since 1943, there were 92 per cent survivors with negative sputum The operative mortality was 4 5 per cent In 111 excisions reviewed by Janes (83) 66 per cent of patients were well, 13.5 per cent were still under treatment, and 16 per cent had died Day *et al* (84) report on 98 lobectomies and 104 pneumonectomies for tuberculosis performed for the usual indications Of the 177 living patients 68 per cent were well In all these series cases usually represented failure of previous therapeutic procedures From this point of view the results may be considered satisfactory There is now, however, a growing tendency to extend the indications of pulmonary resection to include small localized lesions which can be excised with little or no loss of uninvolved

lung tissue. There is no doubt that this approach to excision is feasible, especially in conjunction with chemotherapy, and that the complications and mortality are low [Bickford *et al.* (85)]. But it cannot be overemphasized that the prognosis of localized lesions without excision is relatively good, and the wisdom of their excision can be assessed only after a rather long follow-up period.

Tuberculous Pleurisy with Effusion

The seriousness of primary tuberculous pleurisy with effusion in terms of its late prognosis is often unappreciated. Tuberculous pleurisy with effusion is now generally considered a manifestation of progressive primary infection, and as such, is to be regarded with concern because of the frequency with which tuberculosis subsequently develops in the lungs or other organs. In an excellent article Frostad (86) reports data on 720 cases of primary tuberculous pleurisy followed for 13 years. During this period there was a tuberculous morbidity of 20.6 per cent and a tuberculous mortality of 9.2 per cent Most of the cases of tuberculosis developed within the first five years after the onset of the pleurisy. According to Frostad the prognosis of patients with small effusions and large effusions was similar This point cannot be overemphasized since there is a natural tendency to treat lightly the small transient effusions which are accompanied by minimal symptomatology. Falk (87), in reviewing the recent literature, finds the incidence of tuberculosis following idiopathic tuberculous pleurisy with effusion to be between 21 and 41 per cent The largest number of cases occur within the first two years after the effusion The mortality due to tuberculosis in the five year period was estimated to be 10 per cent, but varied greatly in different series, according to factors such as race and economic status In a study of 200 consecutive cases of primary tuberculous effusion, Sibley (88) reports a tuberculous morbidity of 51 per cent during the post-effusion period. Evidence of hematogeneous dissemination occurred in 18.5 per cent of cases. Sibley's data confirm the observation of Frostad (86) that the size of the effusion bears no relationship to the ultimate prognosis Asserting that tuberculous pleurisy may have a "dry" phase, Sibley advises serial chest films and repeated tuberculin testing of individuals who complain of intermittent chest pain without obvious cause The prognosis of primary tuberculous effusion is so serious that clinical trials with chemotherapy are indicated. Because pleurisy with effusion is so frequently associated with extra-pulmonary lesions, prolonged chemotherapy, possibly for one year, would appear to be the most promising approach. Moreover, in an investigation of this kind the value of chemotherapy cannot be adequately assessed in less than five years, since, in contrast to the late prognosis, the immediate prognosis of the effusion is excellent under any circumstances

Spontaneous Pneumothorax and Hemopneumothorax

A number of articles on spontaneous pneumothorax and hemopneumothorax appeared during the past year. There is now general agreement that

in the vast majority of cases tuberculosis is not an etiologic factor. Excellent reviews emphasizing this point were presented by Hyde & Hyde (89) and Melrose (90). One has the impression from the literature that spontaneous pneumothorax is being treated by surgical methods much more than previously. Hughes *et al.* (91) report 40 cases, 27 of which were treated by closed thoracotomy drainage with excellent results. They point out that intercostal suction is a safe procedure which results in a more rapid re-expansion of the lung and that, in addition, the aseptic pleuritic reaction produced by the catheter may prevent recurrences Bernard & Meyer (92), who have observed 100 cases of non-tuberculous spontaneous pneumothorax since 1945, advocate talc instillations in the pleural space when the pneumothorax is due to emphysematous vesicles. When a large cyst is the cause, they advise thoracotomy and resection of the cyst-bearing lung. In some cases of chronic pneumothorax in which after a number of recurrences the pleural surface is covered with a layer of organized fibrin, decortication is a safe and satisfactory procedure The etiology and treatment of chronic spontaneous pneumothorax is also discussed by Dolley & Brewer (93). They believe that chronic spontaneous pneumothorax is due to the rupture of congenital cysts, pleural cysts, or emphysematous bullae, and advise excision of these along with decortication if a pleural deposit is present. In this series of 22 cases, intrapleural adhesions were seen in 11 In their opinion these prevent complete pulmonary collapse, but are very probably not directly responsible for the spontaneous pneumothorax

Active therapy for spontaneous hemopneumothorax is discussed by Moser (94) who reports four cases treated by frequent aspirations of blood It was his impression that such aspirations did not cause further hemorrhage. All patients had complete expansion of the lung. This rational approach to the treatment of spontaneous hemopneumothorax appears to be an adaptation of the experience gained during the last war in the treatment of traumatic hemothorax Arst *et al* (95) also stress the value of prompt evacuation of blood from the pleural space and the restoration of blood volume by transfusion Myers *et al* (96) state that the occasional case of spontaneous hemopneumothorax requires a thoracotomy, and Deiss *et al.* (97) report two cases, one treated by thoracotomy and decortication, and the other by frequent aspirations of blood. It is clear that the assessibility of thoracic surgeons, the availability of blood for transfusions, and increased realization of the deleterious effect of organized blood in the pleural cavity have modified the approach to the treatment of spontaneous hemopneumothorax

Air Cysts of the Lung

Large air cysts of the lung are now being recognized with greater frequency, and improvements in anesthesia and surgical techniques and the availability of antibiotics have made it possible to remove many of these with excellent results. These bullae may cause dyspnea, cough, chest pain, mediastinal herniation, and, occasionally, fatal asphyxia Infection of both the cyst and the pleural space occurs Modern surgical therapy consists of

removal of the bullae by as limited a resection as possible in order to conserve functioning lung tissue. In a very excellent article Baldwin *et al.* (98) present a physiological classification of air cysts based upon an exhaustive study of 16 cases. They point out that the character of the respiratory dysfunction associated with large cysts depends upon the nature of the bronchial communications, and upon the presence or absence of chronic emphysema. Those bullae with free bronchial communications cause hyperventilation of a large dead space without interfering appreciably with the function of the uninvolved portions of the lung. In these cases surgery is indicated only when there is a significant disturbance of respiratory function. Bullae, however, with intermittent bronchial communications may cause compression of healthy lung tissue and displacement of the mediastinum. The excision of this variety is mandatory and should be done early. In a third group of patients large air cysts are part of chronic generalized emphysema. If the emphysema in these is severe, surgery is contraindicated. Respiratory function studies may aid materially in determining the operability of these patients. The removal of giant air cysts in two patients is reported by Warring & Lindskog (99). They, also, particularly stress the need for surgical intervention in those cases where potentially good lung tissue is compressed by a cyst, but warn that those patients whose cysts are present as a component of diffuse emphysema should not be subjected to surgery.

Dugan & Sampson (100) report 14 patients treated surgically for giant emphysematous blebs and tension cysts. The operative procedures comprised 10 local excisions, 3 segmental excisions, and 2 lobectomies. Definite improvement occurred in 12 of the 14. They stress the fact that in bilateral cases provisions should be made for catheter drainage of the contralateral hemithorax since blebs distend post-operatively.

Arteriovenous Aneurysm of the Lung

There is an increasing awareness of arteriovenous aneurysms of the lung, since the development of modern surgical techniques have made their removal feasible in a great many instances. Many of these anomalies are brought to notice by routine x-rays of the chest where the shadows they cause may resemble a number of entities. In another group of cases symptoms suggestive of congenital heart disease or polycythemia may prompt the patient to seek medical attention. As pointed out by Salvesen & Marstrander (101) these anomalies are not rare. Surgical removal is often followed by dramatic relief of symptomatology. Pugsley & Janes (102) report a case of bilateral arteriovenous aneurysm treated by bilateral resection. The patient had always been dyspneic and cyanotic, and her chief complaint was vertigo. Symptoms were completely relieved by excision of the anomalous vessels. Lindskog and co-workers (103) report four cases, three of which were treated by lobectomy with complete success. They review the clinical and diagnostic features of the syndrome and point out that well-developed arteriovenous aneurysms may be present in the absence of cyanosis, poly-

cythemia, or other symptoms This paper is illustrated by photographs of excellent vinylite casts of the excised aneurysms. In one case there were two distinct aneurysmal sacs, in the others single sacs are found. Vessels from more than one bronchopulmonary segment were sometimes involved in the aneurysm, but no significant contribution from the bronchial arteries was noted. The chief roentgenographic features of these anomalies, according to these authors, are saccular, cirsoid, or racemose sharply defined shadows of homogeneous density which are in association with enlarged tributary vascular channels They emphasize the need for the conservation of lung tissue in the operative procedures since the lesions are not infrequently multiple The use of planigraphy in the demonstration of arteriovenous aneurysms is convincingly illustrated by Salvesen & Marstrander (101) A comprehensive monograph by Giampalmo (104) deserves careful reading by those interested in this subject.

Streptokinase and Streptodornase

One of the most interesting recent advances in the therapy of chest diseases has been the development of the enzymes, streptokinase and streptodornase, for clinical use The lytic activity of streptokinase and streptodornase, sometimes referred to as "enzymatic débridement," is directed against the proteins, fibrin and desoxyribonucleoprotein respectively Their action is to reduce these proteins to a soluble state so that they may be aspirated through a needle or catheter This change in the physical state of the clotted blood or pus also exposes bacteria to the action of antibiotics. Tillett *et al* (105) discuss the use of these agents in 25 patients with post-pneumonic empyema Streptokinase-streptodornase, 200,000 units and 60,000 units respectively, in a 20 cc solution were instilled in the pleural space Twelve to 18 hours afterwards a thorough thoracentesis was done to remove the pus and permit expansion of the lung Additional injections of the enzymes were made two to four days later if residual deposits were present, or when cultures remained positive Twenty-one of the patients were treated with one or more such injections with complete evacuation of the empyema fluid and re-expansion of the lung When empyemata were treated late, viz, the 30th day of the disease, enzymatic activity was not effective since organization had already taken place. Opening of a bronchopleural fistula was noted in one case. In the authors' experience the pyrogenic reactions which occur after the use of streptokinase-streptodornase are controlled by aminopyrine on the day preceding and day following an injection Tillett and co-workers (106) also report the use of streptokinase-streptodornase in 10 patients with chronic empyemata Nine of these were tuberculous Here the method of administration was different from that used in post-pneumonic empyemata. Streptokinase-streptodornase was injected intrapleurally daily for four or five days, and daily drainage was carried out A course of daily injections and aspirations was repeated as long as an increase in the amount of exudate resulted In five cases treated with

streptokinase-streptodornase, *four were healed while the fifth had no benefit*. One relapsed in six months; three remained healed from six months to one year. Of five cases treated with streptokinase-streptodornase plus surgery, three were healed, one had a partial effect and one had no benefit. These authors feel that streptokinase-streptodornase may be definitive therapy in certain cases of chronic empyemata, while in others it must be used only as an adjunct to surgical procedures indicated by the underlying disease. There is no way of predicting on the basis of the duration of the infection which cases will be sterilized by the action of streptokinase-streptodornase Read & Berry (107) report the use of streptokinase-streptodornase in the lysis of blood clots in two cases, one with a hemopneumothorax, the other with a post-pneumonectomy collection of blood. The latter patient had an infected hemothorax, and antibiotics were used in conjunction with the enzymes. The use of these enzymes in hemothorax was further reported by Sherry *et al.* (108). This report includes 10 patients with massive sterile hemothorax after pneumonectomy, four patients with infected hemothorax after pneumonectomy, nine with traumatic hemothorax, and two with infected traumatic hemothorax. Favorable results were obtained in almost every case. The use of streptokinase-streptodornase in the treatment of extrapleural hematoma following extrapleural pneumonolysis in three cases is reported by Gaensler & Streider (109). Complete liquefaction of the clot occurred, and maintenance of an adequate pneumothorax was made possible. Successful employment of streptokinase in treating a hemothorax complicating artificial intrapleural pneumothorax is reported by Gauld & Harold (110). The indications for streptokinase-streptodornase appear to be well-defined in cases of postpneumonic (pneumococci) empyema. While the enzymes are undoubtedly useful in some cases of mixed empyemata, many details need to be worked out, especially in those empyemata associated with tuberculous infection and bronchopleural fistulae. In the treatment of hemothorax the indications are somewhat less certain. The excellent results which may be obtained by the simple, thorough aspiration of blood should not be lost sight of; nor should surgical principles in the treatment of traumatic hemothorax be neglected

ACTH and Cortisone in Chronic Respiratory Disease

Many articles on the use of cortisone and adrenocorticotropic hormone (ACTH) in bronchial asthma appeared in the literature during the past year. Dramatic relief, frequently in a matter of hours or days, is reported by Carryer *et al.* (111) and Carey *et al* (112). Relapses occur but retreatment with cortisone is again effective Carey *et al.* (112) report beneficial results in 19 of 23 patients with remissions lasting from 3 days to 10 months with an average of 68 days. In their experience, ACTH is more effective than cortisone, a point in agreement with Randol & Rollins (113). The effectiveness of these agents did not seem related either to the duration of the asthma or to its etiology. Salt and water retention as a complication of cortisone therapy in asthma is reported by Lowell (114). The use of aerosol-cortisone in the

treatment of bronchial asthma is described by Gelfand (115). He reports beneficial results in four of five cases of both the intrinsic and the extrinsic types Relapses occurred in three of the four patients, but responded to retreatment. The dosage of cortisone in this study was 50 mg. per day for 14 days. No undesirable effects of the hormone were observed.

Lukas' experience (116) with nine patients with chronic pulmonary disease of various kinds treated with ACTH and cortisone leads him to conclude that improvement occurred only in those patients whose disease was secondary to, or complicated by, bronchiolar functional obstruction. Pulmonary function studies suggested that the hormones exerted a sustained bronchial dilating effect These probably act by decreasing the reactivity of the bronchiolar musculature to allergins and by causing a subsidence of chronic inflammatory changes His data indicate that the hormones have little if any value in advanced cases of obstructive emphysema with marked disturbance of gas exchange. This clinical material included four cases of pulmonary emphysema, one of sarcoidosis, one of interstitial pulmonary fibrosis associated with scleroderma and two of perennial bronchial asthma.

There seems to be no doubt that ACTH and cortisone aggravate the course of experimental tuberculous infection Thus, the studies of D'Arcy Hart & Rees (117) in mice, and those of Spain & Molomut (118) in guinea pigs, and the work of Michael *et al* (119) in albino rats, are all in general agreement that in experimental tuberculosis these hormones cause an increase in the mortality rate, in the number of lesions, and in the number of tubercle bacilli within lesions Block *et al.* (120), in addition, report that cortisone interferes with the therapeutic effect of streptomycin in guinea pigs, and Solotorovsky *et al.* (121) found that protection by vaccination was partially negated by cortisone.

There are few reports on the use of ACTH and cortisone in tuberculosis in man. Two patients were treated with ACTH by Freeman *et al* (122) Defervescence, a marked increase in appetite and sense of well-being, and a decrease in cough and sputum volume occurred directly after administration of the hormone. On x-ray, areas of translucency resembling evacuated abscesses appeared in one case In one patient a definite spread of tuberculosis occurred during the period of ACTH therapy; in the other, extension of disease was questionable Muschenheim and co-workers (123) summarized their experience in seven patients treated with ACTH or cortisone Rapid improvement in the manifestations of acute illness occurred In a laryngeal lesion edema and inflammation subsided 48 hours after hormone administration and by the ninth day 80 per cent of a previously ulcerated area had become covered with epithelium. Decrease in the density of pulmonary lesions was noted in five patients After the withdrawal of hormones, signs and symptoms of acute illness reappeared abruptly, pulmonary lesions returned to their former density, and edema and inflammation of the laryngeal lesion returned. Cutaneous hypersensitivity to tuberculin, which had been reversed in three of six patients, returned slowly No deleterious effect of hormone administration was noted in these patients, and in two patients who came

to autopsy there was no manifest alteration of the histopathology of the lesions. It is clear from these reports that while the hormones remove the symptoms of acute illness, they do not benefit the underlying tuberculous disease. The unfavorable influence of these hormones upon the course of experimental tuberculosis, however, strongly suggests that they be used with caution in tuberculous individuals in whom the hormones may be indicated for associated diseases, such as rheumatoid arthritis.

The treatment of sarcoidosis by ACTH and cortisone is now being attempted in many clinics At this writing, however, reports in the literature are relatively few. Sones *et al* (124) noted marked regression of sarcoid lesions in two patients treated with cortisone Biopsies (lymph nodes, skin, and parotid gland) before and after treatment showed pronounced resolution of lesions. The authors suggest that cortisone may be most effective in the relatively acute case of short duration Small (125) reported beneficial results in three cases of sarcoid treated with 100 mg. of cortisone daily for four to six weeks. In these cases pulmonary function tests paralleled clinical and roentgenographic improvement No follow-up studies were available in this preliminary report One case of generalized sarcoid involving lungs, lymph nodes, skin, muscles, and the uveal tract was treated with ACTH by Renold *et al.* (126) for 15 days. This patient had a steadily decreasing pulmonary reserve prior to therapy With ACTH therapy, clearing of the pulmonary lesions occurred, the vital capacity changed from 850 to 2,450 l. per minute, and the maximum breathing capacity increased from 30 to 71 l. per minute Oxygen saturation of the arterial blood increased from 88 to 96 per cent. In *the patient with sarcoid treated with cortisone* by Lukas (116) obstructive *emphysema was a complication Therapy resulted in a relief of bronchiolar obstruction, but the underlying fibrosis was not affected. Improvement in respiration function was also noted by Galdston et al* (127). *In this case the maximum breathing capacity rose from 70 3 to 106.4 l per minute.* These *preliminary reports do not, of course, include data on relapse following withdrawal of hormone In attempting to assess the results of hormone therapy in sarcoidosis it is necessary to recall that the pathological changes in sarcoid are complex. If an exudative phase preceding the granulomatous changes so characteristic of sarcoid may be postulated, it is conceivable that resolution by ACTH or cortisone administered during this phase might prevent progression of the disease.* It is questionable, however, whether *pulmonary fibrosis can be prevented by any therapy once the granulomata have become well established Sarcoidosis is a fruitful field for investigation. It may be expected that correlations between clinical response, serial biopsy, and function studies during hormone therapy will add materially to our knowledge of this entity.*

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126 [illegible] Maisterrena, J , and Thorn, G W., *New Engl. J.*
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ANNOTATED LIST OF REVIEWS IN MEDICINE

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The following list includes most of the reviews which appeared between January and October, 1951. The majority of these articles come from the literature of clinical medicine, but some are more pertinent to the preclinical sciences. This is necessary if the needs of the clinical investigator and even of some clinicians are to be met. There is an increasing degree of overlapping between clinical science and the preclinical sciences.

Many of the reviews listed here were simply perused, but a good proportion were read in their entirety. The latter applies particularly to such fields as the surgical specialties in which the reviewer is not completely at home. The annotation was made when a given review was read or perused. This has led to some inconsistencies as regards their comparative value. It is hoped that in another year a more systematic evaluation may help to avoid this.

Infectious Diseases

1. "Mechanism of Man's Resistance to Infectious Diseases," Nungester, W. J., *Bact. Revs.*, **15**, 105–29 (1951), 101 references A thoughtful essay.
2. "Progress in Internal Medicine—Infectious Diseases," Reimann, H. A., *Arch. Internal Med.*, **87**, 128–74 (1951), 209 references. A critical survey of all significant literature of 1949 to 1950
3. "The Present Status of Antibiotics in Bacterial Infections," Finland, M., *Bull. N Y. Acad. Med.*, **27**, 199–220 (1951), 63 references. A broad critical discussion
4. "The Present Status of Antibiotics in the Treatment of Protozoan Diseases," Shookhoff, H. B., *Bull N Y Acad. Med.*, **27**, 439–51 (1951), 31 references A brief critical review of the field.
5. "Present Status of Antibiotic Therapy in Viral and Rickettsial Disease," Smadel, J. E, *Bull N.Y Acad. Med.*, **27**, 221–31 (1951), 13 references. A brief consideration of the most recent developments.
6. "Coccidiomycosis: A Review," Burch, G. E., Schwarz, J, and Muth, J., *Am. J. Med. Sci.*, **221**, 89–107 (1951), 187 references A complete review of the subject.
7. "Infectious Mononucleosis," Stevens, J E, Bayrd, E. D., and Heck, F. J., *Am. J Med*, **9**, 202–8 (1951), 28 references. A review of more than 200 cases covering all salient features of the disease.
8. "The Treatment of Purulent Meningitis," Sahs, A. L, *Neurol.*, **1**, 394–409 (1951), 73 references. A review in the form of a detailed outline of therapy.

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9. "Canicola Fever—Review, with Report of Two New Cases," Rosenberg, B. L., *Am. J. Med.*, 11, 75–91 (1951), 143 references. A useful summary of our present knowledge of this leptospira infection.

10. "Syphilis," Beerman, H., Nicholas, J., Ford, W. T., and Buerk, M S., *Arch. Internal Med.*, 87, 278–322, 424–68 (1951), 275 references. A monumental review of the late year's literature presented in a critical manner.

11. "Herpangina: Clinical Studies of a Specific Infectious Disease," Parrott, R H., Ross, S., Burke, F. G., and Rice, E. C., *New Engl. J. Med*, 245, 275–80 (1951), 26 references. An adequate summary of a relatively new disease entity, a common summer illness in children.

12. "Listeria Monocytogenes as the Cause of Disease in Man and Animals, and Its Relation to Infectious Mononucleosis from an Etiological and Immunological Aspect," Girard, K. F., and Murray, E. G. D., *Am. J. Med Sci.*, 221, 343–52 (1951), 70 references. A review of the information which has accumulated in the literature during the past 25 years.

13. "The Chemotherapy of Human Virus Infections," Findlay, G. M., *J. Pharm. Pharmacol.*, 3, 193–214 (1951), 225 references. An excellent review of the literature covering the last few years.

14. "Mucoproteins in Relation to Virus Action," Burnet, F. M., *Physiol. Revs.*, 31, 131–50 (1951), 98 references. A review concerned with hemagglutination and cellular infection by viruses.

15. "Problems of Classification of Poliomyelitis Virus," Jungeblut, C. W., *Arch. Path.*, 52, 18 (1951), 91 references A critical survey of the properties of the poliomyelits virus of interest to the epidemiologist and virologist.

16. "Filterable Forms of Bacteria," Klieneberger-Nobel, E., *Bact. Revs*, 15, 77–103 (1951), 138 references. A summary of the recent revival in interest in a once discredited subject.

17. "The Intermediary Metabolism of the Mycobacteria," Edson, N. L., *Bact. Revs.*, 15, 147–82 (1951), 95 references. An admirable review of new knowledge about the acid-fast bacteria.

DISEASES OF THE GASTROINTESTINAL TRACT

1. "Digestive System," Nasset, E S., *Ann Rev. Physiol.*, 13, 115–32 (1951), 146 references. An excellent summary of recent work of interest to the gastroenterologist as well as the physiologist

2. "Atresias of the Gastrointestinal Tract," Evans, C. H, *Surg Gynecol. Obstet., Intern. Abstracts Surg*, 92, 1–8 (1951), 54 references A brief, nonstatistical review of the data on 1,498 cases included in 1,353 reports in the literature.

3 "The Inhibition of Gastric Secretion A Review," Code, C. F, *Pharm. Rev.* 3, 59–106 (1951), 336 references. A survey of all phases of the subject with special emphasis on possible satisfactory inhibitors of gastric secretion for use in man.

4. "One-Year to Four-Year Follow-Up Examination on 130 Vagotomized Patients," Walters, W, and Belding, H. H., *Ann Surg*, 133, 743–51 (1951), 3 references. A personal summary.

5. "The Effect of Parasympathetic or Sympathetic Denervation on Total Stomach Pouch Secretion in Dogs," Lewis, F. J., *Surgery*, 30, 578–94 (1951), 52 references. A thorough investigation with a complete review of the literature.

6. "Gastric Anatacid and Anti-Secretory Drugs: A Survey Based Primarily on their Effects upon Gastric Secretion in Man," Kirsner, J. B, Palmer, W. L., Levin, E., and Klotz, A. P, *Ann. Internal Med*, 35, 785–811 (1951), 206 references An all inclusive survey of the literature.

7. "Liver," Wilson, J. W., *Ann. Rev. Physiol.*, 13, 133–54 (1951), 146 references A very interesting review written primarily from the point of view of the relation of function to structure in both the organ and its cells.

8. "The Hepatic Artery," Markowitz, J., and Rappaport, A. M., *Phsyiol Revs.*, 31, 188–204 (1951), 105 references A review of the pertinent literature, stemming from the recent discovery that there is provision in the liver to prevent the proliferation of anerobes which find their way into it

9. "Hepatic Amebiasis," DeBaken, M. E., and Ochsner, A., *Surg. Gynecol. Obstet., Intern. Abstracts Surg*, 92, 209–31 (1951), 107 references. Summary of a 20-year experience and analysis of 263 cases

Diseases of the Cardiovascular System

1. "New and Old Definitions of Normal Blood Pressure: Clinical Significance of the Newly Established Limits," Master, A. M., Goldstein, I., and Walters, M. B., *Bull. N.Y. Acad. Med.*, 27, 452–65 (1951), 31 references. A short historical résumé

2 "Blood Volume," Gregersen, M. I., *Ann. Rev. Physiol*, 13, 397–412 (1951), 156 references A brief review of the subject covering the literature of most of the past decade.

3 "Myocardial Metabolism in Congestive Heart Failure," Olson, R. E., and Schwartz, W. B, *Medicine*, 30, 21–41 (1951), 135 references A review of interest to the clinical physiologist and cardiologist.

4. "A Consideration of the Mechanism of Congestive Heart Failure," Burch, G. E, and Ray, C T., *Am Heart J.*, 41, 918–46 (1951), 49 references. A review of the various aspects of the subject considered in critical detail.

5. "The Status of Mercurial Diuretics for the Treatment of Congestive Heart Failure," Batterman, R C., *Am. Heart J*, 42, 311–19 (1951), 22 references A critical survey of the current status of the efficacy and safety of mercurial diuretics.

6. "Ion Exchange Resins in Edema," McChesney, E. W, Dock, W., and Tainter, M L., *Medicine*, 30, 183–95 (1951), 46 references. A fine discussion of a subject of much current interest.

7. "Heart," Burchell, H. B, *Ann. Rev Physiol*, 13, 189–216 (1951), 253 references A fine summary of recent work in this field suited to an investigator in any field concerned with the heart.

8 "The Coronary Circulation in Health and Disease as Studied by Coronary Sinus Catheterization," Bing, R. J., *Bull. N Y. Acad Med*, 27, 407–24 (1951), 36 references An excellent, graphically illustrated summary of the

present status of the subject for the physiologist and clinical investigator.

9. "Pharmacology of the Coronary Circulation," Wegria, R., *Pharm. Rev.*, 3, 197–246 (1951), 190 references. A fine review of all the pertinent literature for the physiologist, pharmacologist, and clinical physiologist.

10. "Chronic Constrictive Pericarditis," White, P. D., *Circulation*, 4, 288–94 (1951), 15 references. A concise summary of the subject.

11. "The Newer Knowledge of Atherosclerosis," Firstbrook, J. B., *Brit. Med. J.*, II, 133–38 (1951), 53 references. An excellent résumé of the present state of the subject.

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